

Fundamental limits to collective concentration sensing in cell populations

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The precision of concentration sensing is improved when cells communicate. Here we derive the physical limits to concentration sensing for cells that communicate over short distances by directly exchanging small molecules (juxtacrine signaling), or over longer distances by secreting and sensing a diffusive messenger molecule (autocrine signaling). In the latter case, we find that the optimal cell spacing can be large, due to a tradeoff between maintaining communication strength and reducing signal cross-correlations. This leads to the surprising result that autocrine signaling allows more precise sensing than juxtacrine signaling for sufficiently large populations. We compare our results to data from a wide variety of communicating cell types.

Single cells sense chemical concentrations with extraordinary precision. In some cases this precision approaches the physical limits set by molecular diffusion [1, 2]. Yet, no cell performs this sensory task in isolation. Cells exist in communities, such as colonies, biofilms, and tissues. Within these communities, cells communicate in diverse ways. Communication mechanisms include the direct exchange of molecules between cells in contact (juxtacrine signaling), and the secretion and detection of diffusible molecules over distances comparable to the cell size or longer (autocrine signaling) [3–6]. This raises the question of whether cell-cell communication improves a cell’s sensory precision, beyond what the cell could achieve alone.

Experiments have shown that cells are more sensitive in groups than they are alone. Groups of neurons [7], lymphocytes [8], and epithelial cells [9] exhibit biased morphological or motile responses to chemical gradients that are too shallow for cells to detect individually. Groups of cell nuclei in fruit fly embryos detect morphogen concentrations with a higher precision than is expected for a single nucleus [10–12]. In some of these cases, such as with epithelial cells [9], cell-cell communication has been shown to be directly responsible for the enhanced sensitivity. Yet, from a theoretical perspective, the fundamental limits to concentration sensing have been largely limited to single receptors or single cells [1, 2, 13–17]. Analogous limits for groups of communicating cells have been derived only for specific geometries [18], and are otherwise poorly understood. In particular, it remains unknown whether the limits depend on the communication mechanism (juxtacrine vs. autocrine), and how they scale with collective properties like communication strength and population size.

Here we derive the fundamental limits to the precision of collective sensing by one-, two-, and three-dimensional (3D) populations of cells. We focus on the basic task of sensing a uniform chemical concentration. We compare two ubiquitous communication mechanisms, juxtacrine signaling and autocrine signaling. Intuitively one ex-

pects that sensory precision is enhanced by communication, that communication is strongest when cells are close together, and therefore that juxtacrine signaling should result in the higher sensory precision. Instead, we find that under a broad range of conditions, autocrine signaling results in the higher sensory precision. In fact, we find that for autocrine signaling, it is not optimal for cells to be as close as possible. Rather, an optimal cell-to-cell distance emerges due to a tradeoff between maintaining sufficient communication strength and minimizing signal cross-correlations. For sufficiently large populations, this distance can be many times the cell diameter, meaning that these populations are porous, not tightly packed. Surprisingly, the sensory precision in these porous populations is then higher than that in the case of juxtacrine signaling, where cells are adjacent and communicate directly. We discuss the implications of these findings for cell populations, compare our results to data from a wide variety of communicating cell types, and make predictions for future experiments.

We begin by modeling a single cell in the presence of a diffusible ligand. This will recapitulate the celebrated result of Berg and Purcell [1], and establish the baseline with which collective sensory precision should be compared. Consider a ligand whose concentration $c(\vec{x}, t)$ obeys the three-dimensional diffusion equation $\dot{c} = D_c \nabla^2 c + \eta_c$ with coefficient D_c [19]. The Langevin noise η_c describes fluctuations around the uniform steady-state profile $\bar{c}(\vec{x}) = \bar{c}$, and obeys [20]

$$\langle \eta_c(\vec{x}, t) \eta_c(\vec{x}', t') \rangle = 2D_c \bar{c} \delta(t - t') \vec{\nabla}_x \cdot \vec{\nabla}_{x'} \delta^3(\vec{x} - \vec{x}'). \quad (1)$$

Linearizing as $c(\vec{x}, t) = \bar{c} + \delta c(\vec{x}, t)$ and Fourier transforming in space and time allows us to calculate the power spectrum (see Appendix A), $S_c(\vec{k}, \omega) = 2D_c \bar{c} k^2 / [(D_c k^2)^2 + \omega^2]$, which has the expected form for spatial white noise [21].

We first imagine the cell as a permeable sphere of radius a that counts the number $n(t) = \int_V d^3x c(\vec{x}, t)$ of ligand molecules within its volume V (Fig. 1A), equivalent to Berg and Purcell’s “perfect instrument” [1]. We obtain the power spectrum of n from $S_c(\vec{k}, \omega)$ in Fourier space via contour integration (Appendix A) as $S_n(\omega) = 8\pi \bar{c} a^5 D_c^{-1} f(a\sqrt{2}|\omega|/D_c)$, where $f(y) \equiv$

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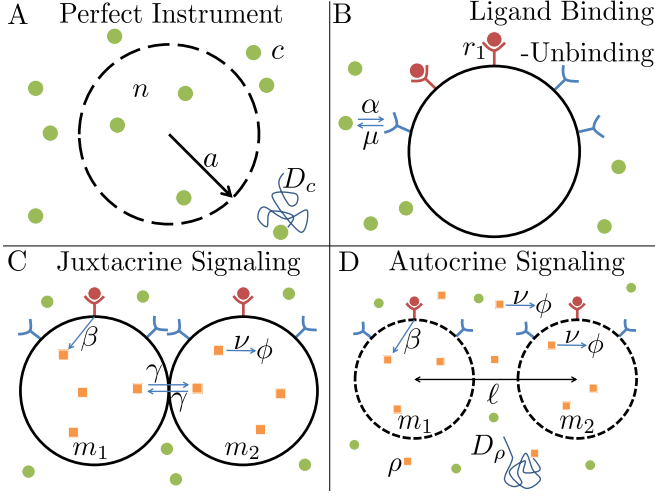


FIG. 1: Isolated (A, B) or communicating (C, D) cells sensing a uniform ligand concentration.

$y^{-5} [e^{-y} \cos y (y^2 + 4y + 2) + (1 + e^{-y} \sin y) (y^2 - 2)]$. This expression has two intuitive limits (Appendix A): first, the instantaneous variance in n is given by $\sigma_n^2 = (2\pi)^{-1} \int_{-\infty}^{\infty} d\omega S_n(\omega) = 4\pi a^3 \bar{c}/3 = \bar{n}$, which reflects the fact that the number of ligand molecules inside the sphere is Poisson-distributed, and therefore the variance equals the mean. Second, the variance $(\delta n)^2$ in the long-time average $T^{-1} \int_0^T dt n(t)$ satisfies

$$\left(\frac{\delta n}{\bar{n}}\right)^2 = \frac{1}{\bar{n}^2} \frac{S_n(0)}{T} = \frac{3}{5} \frac{1}{\pi a \bar{c} D_c T}, \quad (2)$$

where $T \gg \tau_1$ is the integration time, and $\tau_1 \equiv a^2/D_c$ is the characteristic diffusion timescale. Eq. 2 (including the prefactor 3/5) is the well-known Berg-Purcell limit for the perfect instrument [1], and reflects the fact that the variance is reduced by the number T/τ_1 of independent measurements made. From here on we focus on the statistics of long-time averages as in Eq. 2, which we call the *error*, and we continue to take the integration time T longer than the intrinsic timescales in the problem.

To account for cell-cell communication, we will first need to model chemical reactions within cells. Therefore, we extend the single-cell model to include binding and unbinding of ligand molecules to receptors (Fig. 1B):

$$\dot{c} = D_c \nabla^2 c - \sum_{i=1}^N \delta(\vec{x} - \vec{x}_i) \dot{r}_i + \eta_c, \quad (3)$$

$$\dot{r}_i = \alpha c(\vec{x}_i, t) - \mu r_i + \eta_{ri}, \quad (4)$$

Here $N = 1$ for a single cell, which is located at position \vec{x}_1 and acts as a sink and source of ligand molecules as they bind and unbind with rates α and μ , respectively. $r_1(t)$ is the number of bound receptors, and we neglect the effects of receptor saturation. The binding noise η_{ri} obeys [22] $\langle \eta_{ri}(t) \eta_{rj}(t') \rangle = 2\mu \bar{r} \delta_{ij} \delta(t - t')$, where $\bar{r} =$

$\alpha \bar{c}/\mu$ is the mean bound receptor number in steady state. Fourier transforming yields the power spectrum $S_r(\omega)$, from which we obtain the error (see Appendix B)

$$\left(\frac{\delta r}{\bar{r}}\right)^2 = \frac{1}{2} \frac{1}{\pi a \bar{c} D_c T} + \frac{2}{\mu \bar{r} T}, \quad (5)$$

where $T \gg \{\tau_1, \tau_2\}$, and $\tau_2 \equiv \mu^{-1} + (k_D K_D)^{-1}$ is the receptor equilibration timescale, including rebinding events with diffusion-limited rate $k_D = \pi g a D_c$ and dissociation constant $K_D = \mu/\alpha$ [13]. In deriving Eq. 5, we have cut off the wavevector integrals at the maximal value $k = 2\pi/(ga)$ to regularize the divergence caused by the delta function in Eq. 3 [2, 18]. Here g is a geometric factor of order unity that depends on the shape of the cell. In Eq. 5 we have taken $g = 4$ corresponding to the diffusion limited rate $k_D = 4\pi a D_c$ for a sphere of radius a . Eq. 5 can be equivalently derived using the fluctuation dissipation theorem [2, 18], but instead we use the noise prescription in Eq. 1 in order to extend our analysis to non-equilibrium systems with communication. The first term of Eq. 5 is the extrinsic noise arising from diffusive ligand fluctuations. It has the same form as Eq. 2. The second term in Eq. 5 is the intrinsic noise arising from the finite number of bound receptors \bar{r} . In the limit of many bound receptors, this term vanishes. From here on we consider this limit of vanishing intrinsic noise, focusing only on the extrinsic noise, since extrinsic factors such as \bar{c} and D_c are not under direct control of the cell.

We now consider cell-cell communication among N cells, beginning with juxtacrine signaling (Fig. 1C). We retain Eqs. 3 and 4 and introduce a messenger molecule that is exchanged between neighboring cells:

$$\dot{m}_i = \beta r_i - \nu m_i + \gamma \sum_{j \in \mathcal{N}_i} (m_j - m_i) + \eta_{mi}. \quad (6)$$

Here $m_i(t)$ is the number of messenger molecules in cell i . Messenger molecules are produced by bound receptors at a rate β , are degraded at a rate ν , and are exchanged with neighboring cells (denoted by \mathcal{N}_i) at a rate γ . The noise terms obey [22] $\langle \eta_{ri}(t) \eta_{rj}(t') \rangle = 2\mu \bar{r} \delta_{ij} \delta(t - t')$ and $\langle \eta_{mi}(t) \eta_{mj}(t') \rangle = 2\bar{m} M_{ij} \delta(t - t')$, where $\bar{m} = \beta \bar{r}/\nu$ is the mean messenger molecule number per cell in steady state. The matrix $M_{ij} = (\nu + |\mathcal{N}_i| \gamma) \delta_{ij} - \gamma \delta_{j \in \mathcal{N}_i}$, where $|\mathcal{N}_i|$ is the number of neighbors, accounts for the Poisson reaction noise (first term) and the anti-correlations from the exchange (second term). Using the same method as above, we exactly solve for the error for any configuration of cells (see Appendix C). For the special case of $N = 2$ (as in Fig. 1C) the result for the extrinsic noise is

$$\left(\frac{\delta m}{\bar{m}}\right)^2 = \frac{1}{2} \left[1 - \frac{\hat{\lambda}^2(1 + \hat{\lambda}^2)}{(1 + 2\hat{\lambda}^2)^2} \right] \frac{1}{\pi a \bar{c} D_c T} \quad (7)$$

$$\rightarrow \frac{3}{8} \frac{1}{\pi a \bar{c} D_c T} \quad \lambda \gg a, \quad (8)$$

where $T \gg \{\tau_1, \tau_2, \tau_3\}$, and $\tau_3 \equiv (\nu + \gamma)^{-1}$ is the turnover timescale of the messenger molecule. Here $\hat{\lambda} \equiv \lambda/(2a)$,

where $\lambda \equiv 2a\sqrt{\gamma/\nu}$ is the communication length: it is the lengthscale of the exponential kernel that governs the exchange of messenger molecules [9, 18?]. The prefactor in Eq. 7 is a monotonically decreasing function of $\hat{\lambda}$, which demonstrates that noise decreases with increasing communication. In the limit of weak communication $\lambda \ll a$, the prefactor becomes 1/2 as in the one-cell case (Eq. 5). In the limit of strong communication $\lambda \gg a$, it becomes 3/8 (Eq. 8). The fact that 3/8 is larger than half of 1/2 means that two cells are less than twice as good as one cell in terms of sensory precision, even with perfect communication. The reason is that, with juxtacrine signaling, the cells are sampling adjacent regions of extracellular space, and correlations mediated by the diffusing ligand molecules prevent their measurements from being independent [18]. Can autocrine signaling avoid this drawback?

To answer this question, we consider autocrine signaling (Fig. 1D). The autocrine model retains Eqs. 3 and 4 and replaces Eq. 6 with

$$\dot{\rho} = D_\rho \nabla^2 \rho - \nu \rho + \sum_{i=1}^N \delta(\vec{x} - \vec{x}_i) (\beta r_i + \eta_{pi}) + \eta_d. \quad (9)$$

Here $\rho(\vec{x}, t)$ is the concentration of the messenger molecule. Like in Eq. 6, it is produced by each cell at rate β and degraded at rate ν , but now it diffuses within the extracellular space with coefficient D_ρ . As with the perfect instrument, we imagine that each cell counts the number $m_i(t) = \int_{V_i} d^3x \rho(\vec{x}, t)$ of messenger molecules within its volume V_i . The production noise obeys [22] $\langle \eta_{pi}(t) \eta_{pj}(t') \rangle = \beta \bar{r} \delta_{ij} \delta(t - t')$, while the degradation and diffusion noise obeys [20] $\langle \eta_d(\vec{x}, t) \eta_d(\vec{x}', t') \rangle = \nu \bar{\rho}(\vec{x}) \delta(t - t') \delta(\vec{x} - \vec{x}') + 2D_\rho \delta(t - t') \vec{\nabla}_x \cdot \vec{\nabla}_{x'} [\bar{\rho}(\vec{x}) \delta(\vec{x} - \vec{x}')]$. Here

$$\bar{\rho}(\vec{x}) = \frac{\beta \bar{r}}{4\pi D_\rho} \sum_{i=1}^N \frac{e^{-|\vec{x} - \vec{x}_i|/\lambda}}{|\vec{x} - \vec{x}_i|} \quad (10)$$

is the steady-state concentration profile of the messenger molecule, which is non-uniform due to the multiple cell sources. $\lambda \equiv \sqrt{D_\rho/\nu}$ sets the communication length in the autocrine case. As above, we exactly solve for the error for any configuration of cells (see Appendix D). For the special case of $N = 2$ cells separated by a distance ℓ (as in Fig. 1D), in the limit of strong communication $\lambda \gg a$, the result for the extrinsic noise is

$$\left(\frac{\delta m}{\bar{m}} \right)^2 = \frac{1 + \Lambda^2(\hat{\ell}) + 2\Lambda(\hat{\ell})/\hat{\ell}}{2[1 + \Lambda(\hat{\ell})]^2} \frac{1}{\pi a \bar{c} D_c T} \quad (11)$$

$$\rightarrow \frac{2}{5} \frac{1}{\pi a \bar{c} D_c T} \quad \ell = \ell^* = \frac{8}{3} a, \quad (12)$$

where $T \gg \{\tau_1, \tau_2, \tau_4\}$, and $\tau_4 \equiv (\nu + a^2/D_\rho)^{-1}$ is the messenger turnover timescale. Here $\Lambda(\hat{\ell}) \equiv 1 - \hat{\ell}^2/3$ for $\hat{\ell} < 1$, and $2/(3\hat{\ell})$ for $\hat{\ell} > 1$. It is a continuous, monotonically decreasing function of $\hat{\ell} \equiv \ell/a$. Hence, the denominator in Eq. 11 decreases with ℓ ; this is because the

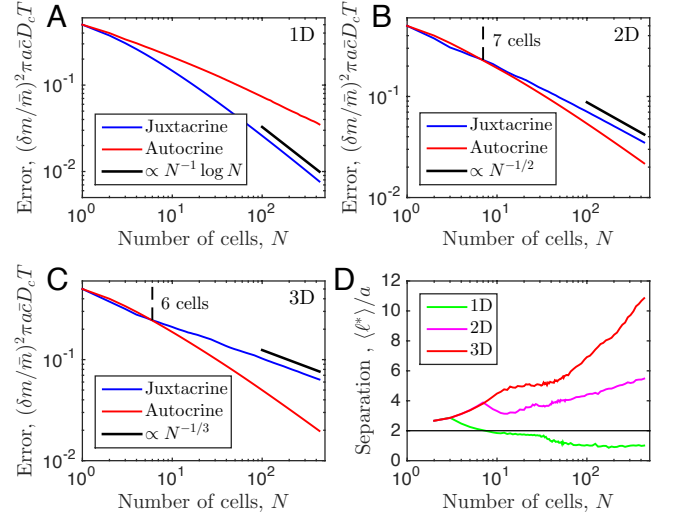


FIG. 2: (A-C) Error in concentration sensing for the two communication strategies vs. the size of 1D, 2D and 3D populations. (D) Average optimal nearest-neighbor separation in the autocrine case. $\langle \ell^* \rangle < 2a$ corresponds to overlapping cells.

mean decreases with cell separation due to the decay of the messenger molecule concentration profile (Eq. 10). The numerator in Eq. 11 also decreases with ℓ ; this is once again because the cells are sampling nearby regions of extracellular space, and the variance decreases with their separation as their measurements become more independent. The tradeoff between these effects results in a minimum value of the prefactor equal to 2/5, when $\ell = \ell^* = 8a/3$ (Eq. 12).

Evidently, for $N = 2$ cells autocrine signaling has improved the precision of concentration sensing less than juxtacrine signaling has ($2/5 > 3/8$). Do the results change for larger N ? Because we have exact results for arbitrary N and arbitrary cell positions (Appendices C and D), we can answer this question immediately. Fig. 2A, B, and C compare as a function of N the error of the two communication mechanisms in the limit of strong communication for 1D, 2D, and 3D configurations of cells, respectively. For juxtacrine signaling, cells are arranged within a line (1D), circle (2D), or sphere (3D) on a rectangular lattice with spacing $2a$. For autocrine signaling, cells are confined to the respective dimensionality, but are otherwise allowed to adjust their positions via a Monte Carlo scheme until the minimum error is reached. The average nearest-neighbor separation $\langle \ell^* \rangle$ in this case is shown in Fig. 2D. We see in Fig. 2A-C that the error always decreases with N , meaning that communication among an increasing number of cells monotonically improves sensory precision. In 1D, we see that juxtacrine signaling results in a smaller error than autocrine signaling for all N (Fig. 2A). In fact, in the case of autocrine signaling in 1D, the optimal separation decreases with N , and beyond $N = 7$, cells overlap, $\langle \ell^* \rangle < 2a$ (Fig.

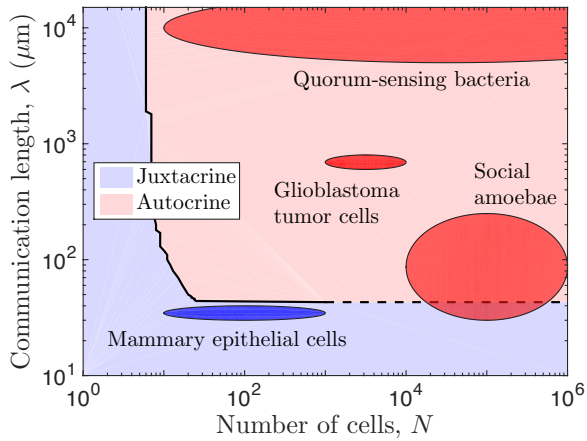


FIG. 3: Phase plot showing the communication strategy that results in the lower error in 3D with $a = 10 \mu\text{m}$, along with estimates from biological systems described in the text. Dashed line is extrapolated from largest numerically tractable N .

2D). However, in 2D and 3D, autocrine signaling results in the smaller error beyond $N = 7$ and $N = 6$ cells, respectively (Fig. 2B and C), and the optimal separation increases with N (Fig. 2D). By $N = 400$ cells, the optimal separation in 3D becomes more than 10 cell radii, meaning that the optimal arrangement of cells is highly “porous”.

It is clear from Fig. 2A-C that the errors of the two communication strategies scale differently with population size. The scaling in the juxtacrine case can be understood quantitatively. In the limit of strong communication, the entire population of contiguous cells acts as one large detector. The error of a long ellipsoidal (1D), disk-shaped (2D), or spherical detector (3D) scales inversely with its longest lengthscale (with a log correction in 1D) [23]. This lengthscale in turn scales with N , $N^{1/2}$, or $N^{1/3}$, respectively, leading to the predicted scalings in Fig. 2A-C, which are seen to agree excellently at large N . On the other hand, the scaling for autocrine signaling is different from that for juxtacrine signaling in each dimension. Evidently diffusive communication and non-contiguous arrangement lead to fundamentally different physics of sensing. In particular, in 2D and 3D the autocrine scaling is clearly steeper at large N (Fig. 2B and C), meaning that not only is the autocrine strategy more precise for a sufficiently large population, but more importantly, the improvement in precision will continue to grow with population size.

How do our results compare to actual biological systems? Arguably the most biologically unrealistic assumption that we make in Fig. 2 is that of strong communication, $\lambda \gg a$. Since our calculations are exact for any λ (Appendices C and D), we relax this assumption in Fig. 3, allowing us to identify phases in the space of λ and N in which either communication strategy is more precise. We now ask where particular biological systems fall

in this phase space. Quorum-sensing bacteria communicate via autocrine signaling with the messenger molecule AHL (among others) [24], for which $D_\rho \sim 490 \mu\text{m}^2/\text{s}$ [25] and $\nu \sim 0.1\text{--}1 \text{ day}^{-1}$ [26, 27], yielding $\lambda \sim 5\text{--}20 \text{ mm}$. Quorum sizes N are typically large but can be as small as tens or hundreds of cells at sufficiently high cell density [28]. Aggregating social amoebae communicate via autocrine signaling with the messenger molecule cAMP [29], for which $D_\rho \sim 300 \mu\text{m}^2/\text{s}$ [30] and $\nu \sim 0.3\text{--}20 \text{ min}^{-1}$ [31, 32], yielding $\lambda \sim 30\text{--}250 \mu\text{m}$. Typical aggregates are $N \sim 10^4\text{--}10^6$ cells [33]. Mammary epithelial cells communicate via juxtacrine signaling across 3–4 cell lengths, or $\lambda \sim 30\text{--}40 \mu\text{m}$ [9]. Typical sensory units at the ends of mammary ducts contain $N \sim 10^1\text{--}10^3$ cells [9, 34]. We see in Fig. 3 that these systems fall within the phases where we would predict that the observed communication strategy of each is the more precise. Of course, bacteria and amoebae are single-cellular, whereas epithelia are multicellular, so one might argue that these strategies are predisposed for other functional reasons. However, many multicellular components adopt porous arrangements and exhibit autocrine signaling. In particular, recent experiments have shown that glioblastoma tumor cells in groups of $N \sim 10^3\text{--}10^4$ secrete the autocrine factors IL-6 and VEGF [35], for which $D_\rho \sim 30 \mu\text{m}^2/\text{s}$ [36] and $100 \mu\text{m}^2/\text{s}$ [37], and $\nu \sim 0.2 \text{ hr}^{-1}$ [38] and 0.7 hr^{-1} [39], respectively, yielding $\lambda \sim 700 \mu\text{m}$. Indeed, in this regime, we would predict that autocrine signaling provides the higher sensory precision (Fig. 3). In fact, in these experiments, cells autonomously adopted a typical spacing of several cell diameters, which the authors argued minimized the signaling noise [35], suggesting a mechanism similar to the one we uncover here.

We have shown that communicating cells maximize the precision of concentration sensing by adopting an optimal separation that can be many cell diameters. This is surprising, since separation weakens the impact of the communication. However, we have demonstrated that cells weigh this drawback against the benefit of obtaining independent measurements of their environment. We predict that the concentration detection threshold for communicating cells should decrease with the cell number, which could be tested using an intracellular fluorescent reporter. Moreover, if cell positions are controllable [35], we predict that a small concentration would be detected by modestly separated cells, but not adjacent or far-apart cells. It will be interesting to test these predictions, as well as to push the theory of collective sensing to further biological contexts.

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Appendix A: Perfect instrument

In this section we consider a single cell as a permeable sphere that counts the number of ligand molecules within its volume. We calculate the power spectra of (i) the ligand concentration and (ii) the number of molecules within the cell, and we calculate both the instantaneous and long-time statistics of the latter.

First, we discuss the correlation function and power spectrum, to establish some definitions and notation. For a one dimensional function $x(t)$, the correlation function $C(t)$ takes the form

$$C(t - t') = \langle x(t') x(t) \rangle. \quad (\text{A1})$$

Since absolute time is irrelevant in any physical system with no time dependent forcing, t' can be set to 0 without

loss of generality. This leads to a definition for the power spectrum of $x(t)$ as

$$\begin{aligned} S(\omega) &= \int \frac{d\omega'}{2\pi} \langle \tilde{x}^*(\omega') \tilde{x}(\omega) \rangle = \frac{1}{2\pi} \int d\omega' dt dt' \langle x(t') x(t) \rangle e^{i\omega t} e^{-i\omega' t'} \\ &= \int dt dt' C(t - t') e^{i\omega t} \delta(t') = \int dt C(t) e^{i\omega t}. \end{aligned} \quad (\text{A2})$$

Thus, under this definition the power spectrum is seen to be the Fourier transform of the correlation function. Additionally, when $x(t)$ is averaged over a time T , the time averaged correlation function of $x(t)$ takes the form

$$\begin{aligned} C_T(t - t') &= \left\langle \left(\frac{1}{T} \int_{t'}^{t'+T} d\tau' x(\tau') \right) \left(\frac{1}{T} \int_t^{t+T} d\tau x(\tau) \right) \right\rangle \\ &= \frac{1}{T^2} \int_t^{t+T} d\tau \int_{t'}^{t'+T} d\tau' \langle x(\tau') x(\tau) \rangle \\ &= \frac{1}{T^2} \int_t^{t+T} d\tau \int_{t'}^{t'+T} d\tau' C(\tau - \tau') \end{aligned} \quad (\text{A3})$$

Let $y \equiv (\tau - \tau') - (t - t')$ and $z \equiv (\tau + \tau') - (t + t')$. This transforms Eq. A3 into

$$\begin{aligned} C_T(t - t') &= \frac{1}{T^2} \int_{-T}^T dy \int_{|y|}^{2T-|y|} dz \frac{1}{2} C(y + t - t') \\ &= \frac{1}{T^2} \int_{-T}^T dy (T - |y|) C(y + t - t'). \end{aligned} \quad (\text{A4})$$

By inverting the relationship found in Eq. A2, $C(y + t - t')$ can be replaced with an inverse Fourier transform of $S(\omega)$ to produce

$$\begin{aligned} C_T(t - t') &= \frac{1}{T^2} \int_{-T}^T dy \int \frac{d\omega}{2\pi} (T - |y|) S(\omega) e^{-i\omega(y+t-t')} \\ &= \int \frac{d\omega}{2\pi} \left(\frac{2}{\omega T} \sin\left(\frac{\omega T}{2}\right) \right)^2 S(\omega) e^{-i\omega(t-t')}. \end{aligned} \quad (\text{A5})$$

The factor of $(\omega T)^{-2}$ in the integrand of Eq. A5 forces only small values of ω to contribute when T is large, implying two possible approximations. First, the approximation $S(\omega) \approx S(0)$ can be made since only values of ω near 0 are contributing. This causes $C_T(0)$ to be exactly calculable to

$$C_T(0) \approx S(0) \int \frac{d\omega}{2\pi} \left(\frac{2}{\omega T} \sin\left(\frac{\omega T}{2}\right) \right)^2 = \frac{S(0)}{T}. \quad (\text{A6})$$

Another possible approximation would be to truncate the limits of integration in Eq. A5 to $[-\omega_T, \omega_T]$. By letting ω_T be small enough such that the $\omega \rightarrow 0$ limit can be assumed for the integrand, $C_T(0)$ can be calculated to be

$$C_T(0) \approx \int_{-\omega_T}^{\omega_T} \frac{d\omega}{2\pi} \lim_{\omega \rightarrow 0} \left(\left(\frac{2}{\omega T} \sin\left(\frac{\omega T}{2}\right) \right)^2 S(\omega) \right) = \frac{\omega_T S(0)}{\pi}. \quad (\text{A7})$$

In order for Eqs. A6 and A7 to be equivalent, $\omega_T = \frac{\pi}{T}$ must be true. Lifting the $\omega \rightarrow 0$ approximation on $S(\omega)$ so the inverse of Eq. A2 is obtained in the $T \rightarrow 0$ limit, the time averaged correlation function for an arbitrary T can be approximated as

$$C_T(t) \approx \int_{-\frac{\pi}{T}}^{\frac{\pi}{T}} \frac{d\omega}{2\pi} \lim_{\omega \rightarrow 0} \left(\left(\frac{2}{\omega T} \sin\left(\frac{\omega T}{2}\right) \right)^2 S(\omega) e^{-i\omega t} \right) = \int_{-\frac{\pi}{T}}^{\frac{\pi}{T}} \frac{d\omega}{2\pi} S(\omega) e^{-i\omega t}. \quad (\text{A8})$$

For the perfect instrument, a ligand species diffuses in a solution via

$$\frac{\partial c}{\partial t} = D_c \nabla^2 c + \eta_c, \quad (\text{A9})$$

where $c(\vec{x}, t)$ is the ligand concentration, D_c is the ligand diffusion constant, and $\eta_c(\vec{x}, t)$ is the noise intrinsic to the diffusion process. This noise has the property

$$\langle \eta_c(\vec{x}', t') \eta_c(\vec{x}, t) \rangle = 2D_c \delta(t - t') \vec{\nabla}_x \cdot \vec{\nabla}_{x'} (\bar{c}(\vec{x}) \delta^3(\vec{x} - \vec{x}')), \quad (\text{A10})$$

where $\bar{c}(\vec{x})$ is the mean value of $c(\vec{x}, t)$ as a function of space, which in this system is taken to be a constant. Performing a Fourier transformation on Eq. A10 then yields

$$\begin{aligned} \langle \tilde{\eta}_c^*(\vec{k}', \omega') \tilde{\eta}_c(\vec{k}, \omega) \rangle &= \int d^3x d^3x' dt dt' \langle \eta_c(\vec{x}', t') \eta_c(\vec{x}, t) \rangle \left(e^{i\vec{k} \cdot \vec{x}} e^{i\omega t} \right) \left(e^{i\vec{k}' \cdot \vec{x}'} e^{i\omega' t'} \right)^* \\ &= \int d^3x d^3x' dt dt' 2D_c \bar{c} e^{i(\vec{k} \cdot \vec{x} - \vec{k}' \cdot \vec{x}')} e^{i(\omega t - \omega' t')} \delta(t - t') \vec{\nabla}_x \cdot \vec{\nabla}_{x'} (\delta^3(\vec{x} - \vec{x}')). \end{aligned} \quad (\text{A11})$$

Due to the factor of $\delta(t - t')$, the integral in t' becomes trivial and leaves the only time dependent factor as $e^{it(\omega - \omega')}$. This allows the integral in t to be solved via the Fourier definition of the d -dimensional δ function

$$\delta^d(\vec{z}) = \int \frac{d^d \kappa}{(2\pi)^d} e^{i\vec{\kappa} \cdot \vec{z}}. \quad (\text{A12})$$

By letting $d = 1$, $\vec{z} = \omega - \omega'$, and $\kappa = t$, utilizing Eq. A12 in Eq. A11 yields

$$\langle \tilde{\eta}_c^*(\vec{k}', \omega') \tilde{\eta}_c(\vec{k}, \omega) \rangle = 2D_c \bar{c} (2\pi \delta(\omega - \omega')) \int d^3x d^3x' e^{i(\vec{k} \cdot \vec{x} - \vec{k}' \cdot \vec{x}')} \vec{\nabla}_x \cdot \vec{\nabla}_{x'} (\delta^3(\vec{x} - \vec{x}')). \quad (\text{A13})$$

Eq. A12 can then be put back into Eq. A13 by letting $d = 3$ and $\vec{z} = \vec{x}$ to change the form of $\delta^3(\vec{x} - \vec{x}')$,

$$\begin{aligned} \langle \tilde{\eta}_c^*(\vec{k}', \omega') \tilde{\eta}_c(\vec{k}, \omega) \rangle &= 2D_c \bar{c} (2\pi \delta(\omega - \omega')) \int d^3x d^3x' e^{i(\vec{k} \cdot \vec{x} - \vec{k}' \cdot \vec{x}')} \vec{\nabla}_x \cdot \vec{\nabla}_{x'} \int \frac{d^3 \kappa}{(2\pi)^3} e^{i\vec{\kappa} \cdot (\vec{x} - \vec{x}')} \\ &= \frac{2D_c \bar{c}}{(2\pi)^3} (2\pi \delta(\omega - \omega')) \int d^3x d^3x' d^3 \kappa e^{i\vec{x} \cdot (\vec{k} + \vec{\kappa})} e^{-i\vec{x}' \cdot (\vec{k}' + \vec{\kappa})} \kappa^2. \end{aligned} \quad (\text{A14})$$

Continuing to utilize Eq. A12, all remaining integrals in Eq. A14 either become δ functions or are over δ functions by integrating over x then κ then x' . This yields for the cross spectrum of $\eta_c(\vec{x}, t)$

$$\begin{aligned} \langle \tilde{\eta}_c^*(\vec{k}', \omega') \tilde{\eta}_c(\vec{k}, \omega) \rangle &= 2D_c \bar{c} (2\pi \delta(\omega - \omega')) \int d^3x' d^3 \kappa \delta^3(\vec{k} + \vec{\kappa}) \kappa e^{-i\vec{x}' \cdot (\vec{k}' + \vec{\kappa})} \kappa^2 \\ &= 2D_c \bar{c} k^2 (2\pi \delta(\omega - \omega')) \int d^3x' e^{-i\vec{x}' \cdot (\vec{k}' - \vec{k})} \\ &= 2D_c \bar{c} k^2 (2\pi \delta(\omega - \omega')) \left((2\pi)^3 \delta^3(\vec{k} - \vec{k}') \right). \end{aligned} \quad (\text{A15})$$

Now, let $c(\vec{x}, t) = \bar{c} + \delta c(\vec{x}, t)$. This linearizes Eq. A9 into

$$\frac{\partial \delta c}{\partial t} = D_c \nabla^2 \delta c + \eta_c. \quad (\text{A16})$$

Eq. A16 can then be Fourier transformed into

$$-i\omega \tilde{\delta c} = -D_c k^2 \tilde{\delta c} + \tilde{\eta} \implies \tilde{\delta c} = \frac{\tilde{\eta}}{D_c k^2 - i\omega}. \quad (\text{A17})$$

Utilizing Eq. A17 to solve for the cross spectrum of $\delta c(\vec{x}, t)$ gives the solution

$$\begin{aligned} \langle \tilde{\delta c}^*(\vec{k}', \omega') \tilde{\delta c}(\vec{k}, \omega) \rangle &= \frac{\langle \tilde{\eta}^*(\vec{k}', \omega') \tilde{\eta}(\vec{k}, \omega) \rangle}{(D_c k^2 - i\omega)(D_c k'^2 + i\omega')} \\ &= \frac{2D_c \bar{c} k^2 (2\pi \delta(\omega - \omega')) \left((2\pi)^3 \delta^3(\vec{k} - \vec{k}') \right)}{(D_c k^2 - i\omega)(D_c k'^2 + i\omega')} \\ &= \frac{2D_c \bar{c} k^2 (2\pi \delta(\omega - \omega')) \left((2\pi)^3 \delta^3(\vec{k} - \vec{k}') \right)}{(D_c k^2)^2 + \omega^2}, \end{aligned} \quad (\text{A18})$$

where the last equality stems from letting $\omega = \omega'$ and $\vec{k} = \vec{k}'$, which is forced by the δ functions. Generalizing the definition of $S(\omega)$ found in Eq. A2 to a 4-dimensional system, Eq. A18 gives the power spectrum of $\delta c(\vec{x}, t)$ to be

$$\begin{aligned} S_c(\vec{k}, \omega) &= \int \frac{d^3 k'}{(2\pi)^3} \frac{d\omega'}{2\pi} \left\langle \tilde{\delta c}^*(\vec{k}', \omega') \tilde{\delta c}(\vec{k}, \omega) \right\rangle \\ &= \int \frac{d^3 k'}{(2\pi)^3} \frac{d\omega'}{2\pi} \frac{2D\bar{c}k^2 (2\pi\delta(\omega - \omega')) ((2\pi)^3 \delta^3(\vec{k} - \vec{k}'))}{(Dk^2)^2 + \omega^2} \\ &= \frac{2D\bar{c}k^2}{(Dk^2)^2 + \omega^2}, \end{aligned} \quad (\text{A19})$$

as in the main text.

Now, let $n(t)$ be the number of molecules in a permeable spherical cell of volume V and radius a . $n(t)$ is calculated from $c(\vec{x}, t)$ via

$$n(t) = \int_V d^3 x c(\vec{x}, t). \quad (\text{A20})$$

Once again, let $n(t) = \bar{n} + \delta n(t)$, where \bar{n} is the mean value of $n(t)$. Since \bar{c} is the mean value of $c(\vec{x}, t)$, this implies

$$\bar{n} = \int_V d^3 x \bar{c} = \frac{4}{3}\pi a^3 \bar{c} \implies \delta n(t) = \int_V d^3 x \delta c(\vec{x}, t). \quad (\text{A21})$$

Fourier transforming the second part of Eq. A21 then yields

$$\tilde{\delta n}(\omega) = \int_V d^3 x \int \frac{d^3 k}{(2\pi)^3} \tilde{\delta c}(\vec{k}, \omega) e^{-i\vec{k} \cdot \vec{x}}. \quad (\text{A22})$$

With this and Eq. A18, the cross spectrum of $n(t)$ is calculated to be

$$\begin{aligned} \left\langle \tilde{\delta n}^*(\omega') \tilde{\delta n}(\omega) \right\rangle &= \left\langle \left(\int_V d^3 x' \int \frac{d^3 k'}{(2\pi)^3} \tilde{\delta c}^*(\vec{k}', \omega') e^{i\vec{k}' \cdot \vec{x}'} \right) \left(\int_V d^3 x \int \frac{d^3 k}{(2\pi)^3} \tilde{\delta c}(\vec{k}, \omega) e^{-i\vec{k} \cdot \vec{x}} \right) \right\rangle \\ &= \frac{1}{(2\pi)^6} \int_V d^3 x d^3 x' \int d^3 k d^3 k' \left\langle \tilde{\delta c}^*(\vec{k}', \omega') \tilde{\delta c}(\vec{k}, \omega) \right\rangle e^{-i(\vec{k} \cdot \vec{x} - \vec{k}' \cdot \vec{x}')} \\ &= \frac{2D_c \bar{c}}{(2\pi)^3} (2\pi\delta(\omega - \omega')) \int_V d^3 x d^3 x' \int d^3 k d^3 k' \frac{k^2 \delta^3(\vec{k} - \vec{k}')}{(D_c k^2)^2 + \omega^2} e^{-i(\vec{k} \cdot \vec{x} - \vec{k}' \cdot \vec{x}')} \\ &= \frac{2D_c \bar{c}}{(2\pi)^3} (2\pi\delta(\omega - \omega')) \int_V d^3 x d^3 x' \int d^3 k \frac{k^2}{(D_c k^2)^2 + \omega^2} e^{-i\vec{k} \cdot \vec{x}} e^{i\vec{k} \cdot \vec{x}'}. \end{aligned} \quad (\text{A23})$$

Since the integrations in Eq. A23 are over three dimensional spaces, the expression

$$\int d\Omega_\kappa e^{i\vec{\kappa} \cdot \vec{z}} = 4\pi \frac{\sin(\kappa |\vec{z}|)}{\kappa |\vec{z}|}, \quad (\text{A24})$$

where Ω_κ is the solid angle at radius κ , can be used to solve the solid angle components of the x and x' integrals, yielding

$$\begin{aligned} \left\langle \tilde{\delta n}^*(\omega') \tilde{\delta n}(\omega) \right\rangle &= \frac{4}{\pi} D_c \bar{c} (2\pi\delta(\omega - \omega')) \int_0^a dx dx' \int d^3 k \frac{k^2}{(D_c k^2)^2 + \omega^2} \left(x^2 \frac{\sin(kx)}{kx} \right) \left(x'^2 \frac{\sin(kx')}{kx'} \right) \\ &= \frac{4}{\pi} D_c \bar{c} (2\pi\delta(\omega - \omega')) \int d^3 k \frac{k^2}{(D_c k^2)^2 + \omega^2} \left(\frac{\sin(ka) - ka \cos(ka)}{k^3} \right)^2 \\ &= 16D_c \bar{c} a^2 (2\pi\delta(\omega - \omega')) \int_0^\infty dk \frac{1}{(D_c k^2)^2 + \omega^2} \left(\frac{\sin(ka)}{ka} - \cos(ka) \right)^2. \end{aligned} \quad (\text{A25})$$

To solve this integral, it must first be noted that the integrand is even in k . Thus, the lower limit can be extended to $-\infty$ simply by introducing a factor of $\frac{1}{2}$. Additionally, the sin and cos terms can be broken into their exponential forms to produce

$$\begin{aligned}
& \langle \tilde{\delta n}^*(\omega') \tilde{\delta n}(\omega) \rangle \\
&= 16D_c \bar{c} a^2 (2\pi\delta(\omega - \omega')) \frac{1}{2} \int_{-\infty}^{\infty} dk \frac{1}{(Dk^2)^2 + \omega^2} \left(\frac{1}{2ika} (e^{ika} - e^{-ika}) - \frac{1}{2} (e^{ika} + e^{-ika}) \right)^2 \\
&= 2D_c \bar{c} a^2 (2\pi\delta(\omega - \omega')) \int_{-\infty}^{\infty} dk \frac{1}{(Dk^2)^2 + \omega^2} \left(e^{2ika} \left(1 + \frac{i}{ka}\right)^2 + e^{-2ika} \left(1 - \frac{i}{ka}\right)^2 + 2 \frac{1+k^2 a^2}{k^2 a^2} \right). \quad (\text{A26})
\end{aligned}$$

Note that the integrand in Eq. A26 has four poles at $k = \sqrt{\frac{|\omega|}{D_c}} e^{i\theta}$ for $\theta \in [\frac{\pi}{4}, \frac{3\pi}{4}, \frac{5\pi}{4}, \frac{7\pi}{4}]$. These poles can be used to solve the integral via contour integration. Let C_1 be a counter-clockwise path around the infinite half circle enclosing the upper half plane and C_2 be a clockwise path around the infinite half circle enclosing the lower half plane. This split allows for terms of the form e^{ika} to be integrated around C_1 and terms of the form e^{-ika} to be integrated around C_2 without any divergences. Additionally, this split will cause poles to form at $k = 0$, but since the integrand in Eq. A26 has no poles at $k = 0$ all subsequent $k = 0$ poles must cancel and thus need not be taken into account. With these contours, the residue theorem can be used to produce

$$\begin{aligned}
& \langle \tilde{\delta n}^*(\omega') \tilde{\delta n}(\omega) \rangle \\
&= \frac{2\bar{c}a^2}{D_c} (2\pi\delta(\omega - \omega')) \left(\int_{C_1} dk \frac{e^{2ika} \left(1 + \frac{i}{ka}\right)^2 + 2 \frac{1+k^2 a^2}{k^2 a^2}}{\left(k - \sqrt{\frac{|\omega|}{D_c}} e^{i\frac{\pi}{4}}\right) \left(k - \sqrt{\frac{|\omega|}{D_c}} e^{i\frac{3\pi}{4}}\right) \left(k - \sqrt{\frac{|\omega|}{D_c}} e^{i\frac{5\pi}{4}}\right) \left(k - \sqrt{\frac{|\omega|}{D_c}} e^{i\frac{7\pi}{4}}\right)} \right. \\
&\quad \left. + \int_{C_2} dk \frac{e^{-2ika} \left(1 - \frac{i}{ka}\right)^2}{\left(k - \sqrt{\frac{|\omega|}{D_c}} e^{i\frac{\pi}{4}}\right) \left(k - \sqrt{\frac{|\omega|}{D_c}} e^{i\frac{3\pi}{4}}\right) \left(k - \sqrt{\frac{|\omega|}{D_c}} e^{i\frac{5\pi}{4}}\right) \left(k - \sqrt{\frac{|\omega|}{D_c}} e^{i\frac{7\pi}{4}}\right)} \right) \\
&= \frac{4\pi\bar{c}a^2 i}{D_c} (2\pi\delta(\omega - \omega')) \left(\left. \frac{e^{2ika} \left(1 + \frac{i}{ka}\right)^2 + 2 \frac{1+k^2 a^2}{k^2 a^2}}{\left(k - \sqrt{\frac{|\omega|}{D_c}} e^{i\frac{3\pi}{4}}\right) \left(k - \sqrt{\frac{|\omega|}{D_c}} e^{i\frac{5\pi}{4}}\right) \left(k - \sqrt{\frac{|\omega|}{D_c}} e^{i\frac{7\pi}{4}}\right)} \right|_{k=\sqrt{\frac{|\omega|}{D_c}} e^{i\frac{\pi}{4}}} \right. \\
&\quad + \left. \frac{e^{2ika} \left(1 + \frac{i}{ka}\right)^2 + 2 \frac{1+k^2 a^2}{k^2 a^2}}{\left(k - \sqrt{\frac{|\omega|}{D_c}} e^{i\frac{\pi}{4}}\right) \left(k - \sqrt{\frac{|\omega|}{D_c}} e^{i\frac{5\pi}{4}}\right) \left(k - \sqrt{\frac{|\omega|}{D_c}} e^{i\frac{7\pi}{4}}\right)} \right|_{k=\sqrt{\frac{|\omega|}{D_c}} e^{i\frac{3\pi}{4}}} \\
&\quad - \left. \frac{e^{-2ika} \left(1 - \frac{i}{ka}\right)^2}{\left(k - \sqrt{\frac{|\omega|}{D_c}} e^{i\frac{\pi}{4}}\right) \left(k - \sqrt{\frac{|\omega|}{D_c}} e^{i\frac{3\pi}{4}}\right) \left(k - \sqrt{\frac{|\omega|}{D_c}} e^{i\frac{7\pi}{4}}\right)} \right|_{k=\sqrt{\frac{|\omega|}{D_c}} e^{i\frac{5\pi}{4}}} \\
&\quad - \left. \frac{e^{-2ika} \left(1 - \frac{i}{ka}\right)^2}{\left(k - \sqrt{\frac{|\omega|}{D_c}} e^{i\frac{\pi}{4}}\right) \left(k - \sqrt{\frac{|\omega|}{D_c}} e^{i\frac{3\pi}{4}}\right) \left(k - \sqrt{\frac{|\omega|}{D_c}} e^{i\frac{5\pi}{4}}\right)} \right|_{k=\sqrt{\frac{|\omega|}{D_c}} e^{i\frac{7\pi}{4}}} \right). \quad (\text{A27})
\end{aligned}$$

After some algebraic manipulation of Eq. A27, the final form of the cross spectrum of $n(t)$ is found to be

$$\langle \tilde{\delta n}^*(\omega') \tilde{\delta n}(\omega) \rangle = (2\pi\delta(\omega - \omega')) \frac{16\pi\bar{c}a^5}{15D_c} f\left(a\sqrt{\frac{2|\omega|}{D_c}}\right), \quad (\text{A28})$$

where

$$f(x) \equiv \frac{15}{x^5} \left(e^{-x} \cos(x) \left(\frac{x^2}{2} + 2x + 1 \right) + (1 + e^{-x} \sin(x)) \left(\frac{x^2}{2} - 1 \right) \right). \quad (\text{A29})$$

This allows the power spectrum of $n(t)$ to be written as

$$S_n(\omega) = \int \frac{d\omega'}{2\pi} \langle \tilde{n}^*(\omega') \tilde{n}(\omega) \rangle = \frac{16\pi\bar{c}a^5}{15D_c} f \left(a\sqrt{\frac{2|\omega|}{D_c}} \right), \quad (\text{A30})$$

as in the main text.

The correlation function of $n(t)$ is

$$\begin{aligned} C_n(t) &= \int \frac{d\omega}{2\pi} S_n(\omega) e^{-i\omega t} = \frac{8\bar{c}a^5}{15D_c} \int d\omega f \left(a\sqrt{\frac{2|\omega|}{D_c}} \right) e^{-i\omega t} \\ &= \frac{8\bar{c}a^5}{15D_c} \int_0^\infty d\omega \left(f \left(a\sqrt{\frac{2\omega}{D_c}} \right) e^{-i\omega t} + f \left(a\sqrt{\frac{2\omega}{D_c}} \right) e^{i\omega t} \right) \\ &= \frac{16\bar{c}a^5}{15D_c} \int_0^\infty d\omega f \left(a\sqrt{\frac{2\omega}{D_c}} \right) \cos(\omega t). \end{aligned} \quad (\text{A31})$$

Let $x \equiv a\sqrt{\frac{2\omega}{D_c}}$. This transforms Eq. A31 into

$$C_n(t) = \frac{16\bar{c}a^3}{15} \int_0^\infty dx x f(x) \cos \left(x^2 \frac{D_c t}{2a^2} \right). \quad (\text{A32})$$

While the integral in Eq. A32 is not explicitly doable, several of its most important properties can be determined. First, the instantaneous variance, $C_n(0)$, can be exactly calculated to be

$$\sigma_n^2 = C_n(0) = \frac{16\bar{c}a^3}{15} \int_0^\infty dx x f(x) = \frac{16\bar{c}a^3}{15} \frac{5\pi}{4} = \frac{4}{3} \pi a^3 \bar{c} = \bar{n}, \quad (\text{A33})$$

as in the main text. Thus, the instantaneous variance is seen to be equal to the mean, as expected since diffusion is a Poisson process.

Second, the time averaged correlation function can be obtained by truncating the integral in Eq. A31 at $\frac{\pi}{T}$, as was done for Eq. A8. This is equivalent to changing the upper limit of the integral in Eq. A32 to $b \equiv a\sqrt{\frac{2\pi}{D_c T}}$. While the integral is still not explicitly doable, it can be Taylor expanded around small b , which assumes $T \gg \tau_1 = \frac{a^2}{D_c}$, when t is taken to be 0 again. This expansion, when taken out to the tenth order, takes the form

$$\begin{aligned} C_{n_T}(0) &= \frac{16\bar{c}a^3}{15} \int_0^b dx x f(x) \\ &\approx \frac{16\bar{c}a^3}{15} \left(\frac{1}{2}b^2 - \frac{5}{36}b^3 + \frac{1}{120}b^5 - \frac{5}{2268}b^6 + \frac{1}{3920}b^7 \right. \\ &\quad \left. - \frac{1}{204120}b^9 + \frac{1}{1201200}b^{10} - \dots \right). \end{aligned} \quad (\text{A34})$$

Taking only the first term from Eq. A34, the noise-to-signal ratio is

$$\frac{\sigma_{n_T}^2}{\bar{n}^2} \frac{C_{n_T}(0)}{\bar{n}^2} \approx \frac{\frac{16\bar{c}a^3}{15} \frac{1}{2} \left(a\sqrt{\frac{2\pi}{D_c T}} \right)^2}{\left(\frac{4}{3} \pi a^3 \bar{c} \right)^2} = \frac{3}{5\pi a \bar{c} D_c T}, \quad (\text{A35})$$

as in the main text.

Appendix B: Receptor binding and unbinding

We now assume there is an arbitrary number of cells and each is no longer permeable but rather has a number of receptors covering its surface. The ligand binds and unbinds from the receptors at rates α and μ respectively. The purpose of this section is to calculate the statistics of the long-time average of the number of bound receptors on a particular cell.

Assuming the cells are small enough to be considered point-like relative to the whole system and the number of receptors on each cell is large enough to neglect the effects of increased bound receptor number on the overall binding propensity (i.e. receptor saturation), this system can be modeled via

$$\frac{\partial c}{\partial t} = D_c \nabla^2 c - \sum_j \delta^3(\vec{x} - \vec{x}_j) \frac{\partial r_j}{\partial t} + \eta_c \quad (\text{B1a})$$

$$\frac{\partial r_j}{\partial t} = \alpha c(\vec{x}_j, t) - \mu r_j + \eta_{r_j}, \quad (\text{B1b})$$

where for the j th cell $r_j(t)$ is the number of bound receptors, \vec{x}_j is the position, and $\eta_{r_j}(t)$ is the noise in the binding-unbinding process. Let $r_j(t) = \bar{r}_j + \delta r_j(t)$, where \bar{r}_j is the mean value of $r_j(t)$. Eq. B1b then dictates

$$0 = \alpha \bar{c} - \mu \bar{r}_j \implies \bar{r}_j = \frac{\alpha \bar{c}}{\mu}, \quad (\text{B2})$$

while Eqs. B1 can be written in the form

$$\frac{\partial \delta c}{\partial t} = D_c \nabla^2 \delta c - \sum_j \delta^3(\vec{x} - \vec{x}_j) \frac{\partial \delta r_j}{\partial t} + \eta_c \quad (\text{B3a})$$

$$\frac{\partial \delta r_j}{\partial t} = \alpha \delta c(\vec{x}_j, t) - \mu \delta r_j + \eta_{r_j}. \quad (\text{B3b})$$

Fourier transforming Eq. B3a then yields

$$\begin{aligned} -i\omega \tilde{\delta c} &= -D_c k^2 \tilde{\delta c} - \sum_j e^{i\vec{k} \cdot \vec{x}_j} (-i\omega \tilde{\delta r}_j) + \tilde{\eta}_c \\ \implies \tilde{\delta c} &= \frac{i\omega \sum_j \tilde{\delta r}_j e^{i\vec{k} \cdot \vec{x}_j} + \tilde{\eta}_c}{D_c k^2 - i\omega}. \end{aligned} \quad (\text{B4})$$

Similarly Fourier transforming Eq. B3b then yields

$$\begin{aligned} -i\omega \tilde{\delta r}_j &= \alpha \int \frac{d^3 k}{(2\pi)^3} \tilde{\delta c}(\vec{k}, \omega) e^{-i\vec{k} \cdot \vec{x}_j} - \mu \tilde{\delta r}_j + \tilde{\eta}_{r_j} \\ &= \alpha \int \frac{d^3 k}{(2\pi)^3} \frac{i\omega \sum_l \tilde{\delta r}_l e^{i\vec{k} \cdot \vec{x}_l} + \tilde{\eta}_c}{D_c k^2 - i\omega} e^{-i\vec{k} \cdot \vec{x}_j} - \mu \tilde{\delta r}_j + \tilde{\eta}_{r_j} \\ \implies (\mu - i\omega) \tilde{\delta r}_j - i\omega \sum_l \tilde{\delta r}_l \Sigma(\vec{x}_l - \vec{x}_j, \omega) &= \alpha \int \frac{d^3 k}{(2\pi)^3} \frac{\tilde{\eta}_c}{D_c k^2 - i\omega} e^{-i\vec{k} \cdot \vec{x}_j} + \tilde{\eta}_{r_j}, \end{aligned} \quad (\text{B5})$$

where

$$\Sigma(\vec{x}, \omega) \equiv \alpha \int \frac{d^3 k}{(2\pi)^3} \frac{1}{D_c k^2 - i\omega} e^{i\vec{k} \cdot \vec{x}} = \frac{\alpha}{4\pi D_c |\vec{x}|} e^{-|\vec{x}| \sqrt{\frac{\omega}{2D_c}}} e^{i|\vec{x}| \sqrt{\frac{\omega}{2D_c}}}. \quad (\text{B6})$$

Thus, it is seen that $\Sigma(\vec{x}, \omega)$ is dependent only on the magnitude of \vec{x} , implying $\Sigma(-\vec{x}, \omega) = \Sigma(\vec{x}, \omega)$.

Unfortunately, $\Sigma(\vec{x}, \omega)$ diverges as $\vec{x} \rightarrow 0$. This case can be rectified by truncating the range of integration in Eq. B6 to be inside of a sphere, S , in k space with radius $\frac{2\pi}{ga}$, where a is the cell radius and g is a geometric factor. This

lets $\Sigma(0, \omega)$ to be evaluated as

$$\begin{aligned}\Sigma(0, \omega) &\approx \alpha \int_S \frac{d^3k}{(2\pi)^3} \frac{1}{D_c k^2 - i\omega} \\ &= \frac{\alpha}{\pi g a D_c} \left(1 + \frac{ga}{8\pi} \sqrt{\frac{\omega}{2D_c}} \left(\log \left(\frac{4D_c \pi^2 + \omega g^2 a^2 - 2\pi g a \sqrt{2\omega D_c}}{4D_c \pi^2 + \omega g^2 a^2 + 2\pi g a \sqrt{2\omega D_c}} \right) - 2 \arctan \left(\frac{2\pi g a \sqrt{2\omega D_c}}{\omega g^2 a^2 - 4D_c \pi^2} \right) \right) \right) \\ &\quad + \frac{i\alpha}{2\pi\omega} \left(\frac{|\omega|}{2D_c} \right)^{\frac{3}{2}} \approx \frac{\alpha}{\pi g a D_c} + \frac{i\alpha}{2\pi\omega} \left(\frac{|\omega|}{2D_c} \right)^{\frac{3}{2}},\end{aligned}\tag{B7}$$

where the final approximation was made assuming $\omega a^2 \ll D_c$. This is equivalent to the assumption $T \gg \tau_1 = a^2/D_c$ made in the previous section, i.e. that over a time T the ligand can easily diffuse around the whole cell.

Now, let R be a matrix defined as:

$$R_{jl}(\omega) \equiv \begin{cases} \mu - i\omega(1 + \Sigma(0, \omega)) & j = l \\ -i\omega \Sigma(\vec{x}_j - \vec{x}_l, \omega) & j \neq l \end{cases}.\tag{B8}$$

Since $\Sigma(\vec{x}_j - \vec{x}_l, \omega) = \Sigma(\vec{x}_l - \vec{x}_j, \omega)$, R is seen to be a symmetric matrix. With this, Eq. B5 can be rewritten as

$$\begin{aligned}\sum_l R_{jl}(\omega) \tilde{\delta} r_l &= \alpha \int \frac{d^3k}{(2\pi)^3} \frac{\tilde{\eta}_c}{D_c k^2 - i\omega} e^{-i\vec{k} \cdot \vec{x}_j} + \tilde{\eta}_{rj} \\ \implies \tilde{\delta} r_j &= \sum_l R_{jl}^{-1}(\omega) \left(\alpha \int \frac{d^3k}{(2\pi)^3} \frac{\tilde{\eta}_c}{D_c k^2 - i\omega} e^{-i\vec{k} \cdot \vec{x}_l} + \tilde{\eta}_{rl} \right).\end{aligned}\tag{B9}$$

Utilizing Eq. B9 yields the cross spectrum of $r_j(t)$ and $r_l(r)$ to be

$$\begin{aligned}\langle \tilde{\delta} r_l^*(\omega') \tilde{\delta} r_j(\omega) \rangle &= \left\langle \left(\sum_u R_{lu}^{-1}(\omega') \left(\alpha \int \frac{d^3k'}{(2\pi)^3} \frac{\tilde{\eta}_c(\vec{k}', \omega')}{D_c k'^2 - i\omega'} e^{-i\vec{k}' \cdot \vec{x}_n} + \tilde{\eta}_{ru}(\omega') \right) \right)^* \right. \\ &\quad \cdot \left. \left(\sum_s R_{js}^{-1}(\omega) \left(\alpha \int \frac{d^3k}{(2\pi)^3} \frac{\tilde{\eta}_c(\vec{k}, \omega)}{D_c k^2 - i\omega} e^{-i\vec{k} \cdot \vec{x}_m} + \tilde{\eta}_{rs}(\omega) \right) \right) \right\rangle.\end{aligned}\tag{B10}$$

At this point it is necessary to determine the properties of η_{rj} . Since the binding-unbinding process for a given cell is independent of the binding-unbinding process of any other cell and the ligand diffusion, it must be true that cross correlations between η_{rj} and η_{rl} , for $j \neq l$, or η_c vanish. Additionally, since Eq. B3b is of the form of a birth-death process, the power spectrum of η_{rj} must be the sum of the mean propensities of its reactions. These all imply

$$\begin{aligned}\langle \tilde{\eta}_{rl}^*(\omega'), \tilde{\eta}_{rj}(\omega) \rangle &= (\alpha \bar{c} + \mu \bar{r}_j) \delta_{jl} (2\pi \delta(\omega - \omega')) \\ &= 2\alpha \bar{c} \delta_{jl} (2\pi \delta(\omega - \omega')).\end{aligned}\tag{B11}$$

Ignoring the vanishing cross terms between $\tilde{\eta}_c$ and $\tilde{\eta}_{rj}$ allows Eq. B10 to be written in the form

$$\begin{aligned}\langle \tilde{\delta} r_l^*(\omega') \tilde{\delta} r_j(\omega) \rangle &= \sum_{s,u} R_{js}^{-1}(\omega) (R_{lu}^{-1}(\omega'))^* \left(\langle \tilde{\eta}_{ru}^*(\omega'), \tilde{\eta}_{rs}(\omega) \rangle \right. \\ &\quad \left. + \alpha^2 \int \frac{d^3k d^3k'}{(2\pi)^6} \frac{\langle \tilde{\eta}_c^*(\vec{k}', \omega'), \tilde{\eta}_c(\vec{k}, \omega) \rangle}{(D_c k^2 - i\omega)(D_c k'^2 + i\omega')} e^{i(\vec{k}' \cdot \vec{x}_u - \vec{k} \cdot \vec{x}_s)} \right).\end{aligned}\tag{B12}$$

Utilizing Eqs. A15 and B11 to evaluate the noise correlation terms then yields

$$\begin{aligned}
\langle \tilde{\delta} r_l^* (\omega') \tilde{\delta} r_j (\omega) \rangle &= \sum_{s,u} R_{js}^{-1} (\omega) (R_{lu}^{-1} (\omega'))^* \left(2\alpha \bar{c} \delta_{su} (2\pi \delta (\omega - \omega')) \right. \\
&\quad \left. + \alpha^2 \int \frac{d^3 k d^3 k'}{(2\pi)^6} \frac{2D_c \bar{c} k^2 (2\pi \delta (\omega - \omega')) \left((2\pi)^3 \delta^3 (\vec{k} - \vec{k}') \right)}{(D_c k^2 - i\omega) (D_c k'^2 + i\omega')} e^{i(\vec{k}' \cdot \vec{x}_u - \vec{k} \cdot \vec{x}_s)} \right) \\
&= 2\alpha \bar{c} (2\pi \delta (\omega - \omega')) \sum_{s,u} R_{js}^{-1} (\omega) (R_{lu}^{-1} (\omega))^{*} \left(\delta_{su} + \alpha \int \frac{d^3 k}{(2\pi)^3} \frac{D_c k^2}{(D_c k^2)^2 + \omega^2} e^{i\vec{k} \cdot (\vec{x}_u - \vec{x}_s)} \right), \tag{B13}
\end{aligned}$$

where all instances of ω' outside of the δ function were freely replaced with ω due to the δ function being a global factor. As known from Eq. A24, the angular portion of the integral in Eq. B13 will cause the imaginary component to vanish. Thus, the integral is completely real and may be expressed as the real part of $\Sigma (\vec{x}_u - \vec{x}_s, \omega)$

$$\begin{aligned}
\langle \tilde{\delta} r_l^* (\omega') \tilde{\delta} r_j (\omega) \rangle &= 2\alpha \bar{c} (2\pi \delta (\omega - \omega')) \sum_{s,u} R_{js}^{-1} (\omega) (R_{lu}^{-1} (\omega))^{*} (\delta_{su} + \text{Re} (\Sigma (\vec{x}_u - \vec{x}_s, \omega))). \tag{B14}
\end{aligned}$$

Comparing the last term in Eq. B14 with Eq. B8 then allows Eq. B14 to be written as

$$\langle \tilde{\delta} r_l^* (\omega') \tilde{\delta} r_j (\omega) \rangle = 2\alpha \bar{c} (2\pi \delta (\omega - \omega')) \sum_{s,u} R_{js}^{-1} (\omega) (R_{lu}^{-1} (\omega))^{*} \left(\frac{1}{\omega} \text{Im} ((R_{us} (\omega))^*) \right). \tag{B15}$$

In order to simplify Eq. B15, first let a and b be two arbitrary complex numbers. The product $a \text{Im} (b)$ can be reordered as

$$\begin{aligned}
a \text{Im} (b) &= \text{Re} (a) \text{Im} (b) + i \text{Im} (a) \text{Im} (b) \\
&= (\text{Re} (a) \text{Im} (b) + \text{Im} (a) \text{Re} (b)) - \text{Im} (a) (\text{Re} (b) - i \text{Im} (b)) \\
&= \text{Im} (ab) - b^* \text{Im} (a) = \text{Im} (ab) + b^* \text{Im} (a^*). \tag{B16}
\end{aligned}$$

Applying Eq. B16 to the $(R_{lu}^{-1} (\omega))^* \text{Im} ((R_{us} (\omega))^*)$ term in Eq. B15 yields

$$\begin{aligned}
\langle \tilde{\delta} r_l^* (\omega') \tilde{\delta} r_j (\omega) \rangle &= \frac{2\alpha \bar{c}}{\omega} (2\pi \delta (\omega - \omega')) \sum_{s,u} R_{js}^{-1} (\omega) \\
&\quad \cdot \left(\text{Im} \left((R_{lu}^{-1} (\omega))^* (R_{us} (\omega))^* \right) + R_{us} (\omega) \text{Im} (R_{lu}^{-1} (\omega)) \right). \tag{B17}
\end{aligned}$$

Separating out the sums then yields

$$\begin{aligned}
\langle \tilde{\delta} r_l^* (\omega') \tilde{\delta} r_j (\omega) \rangle &= \frac{2\alpha \bar{c}}{\omega} (2\pi \delta (\omega - \omega')) \left(\sum_s R_{js}^{-1} (\omega) \sum_u \text{Im} \left((R_{lu}^{-1} (\omega) R_{us} (\omega))^* \right) \right. \\
&\quad \left. + \sum_u \text{Im} (R_{lu}^{-1} (\omega)) \sum_s R_{js}^{-1} (\omega) R_{us} (\omega) \right). \tag{B18}
\end{aligned}$$

In the first term of Eq. B18 the summation over n can be brought inside the Im and complex conjugation operators and causes the product $R_{lu}^{-1} (\omega) R_{us} (\omega)$ to collapse to δ_{ls} . However, since the Kronecker δ function is real, its imaginary component must be 0, and thus the whole first term vanishes. In the second term, the fact that R is symmetric can be used to make the substitutions $R_{lu}^{-1} (\omega) \rightarrow R_{ul}^{-1} (\omega)$ and $R_{us} (\omega) \rightarrow R_{su} (\omega)$, which causes Eq. B18 to simplify to

$$\begin{aligned}
\langle \tilde{\delta} r_l^* (\omega') \tilde{\delta} r_j (\omega) \rangle &= \frac{2\alpha \bar{c}}{\omega} (2\pi \delta (\omega - \omega')) \sum_u \text{Im} (R_{ul}^{-1} (\omega)) \sum_s R_{js}^{-1} (\omega) R_{su} (\omega) \\
&= \frac{2\alpha \bar{c}}{\omega} (2\pi \delta (\omega - \omega')) \sum_u \text{Im} (R_{ul}^{-1} (\omega)) \delta_{ju} \\
&= \frac{2\alpha \bar{c}}{\omega} (2\pi \delta (\omega - \omega')) \text{Im} (R_{jl}^{-1} (\omega)). \tag{B19}
\end{aligned}$$

Thus, Eq. B19 can be seen to be formed from the imaginary component of the matrix element used to connect $\tilde{\delta}r_j$ to the noise terms, exactly as would be predicted by the fluctuation-dissipation theorem.

Under the limit $\mu \gg \omega(1 + \Sigma(0, \omega))$, which is equivalent to $\omega \ll (\mu^{-1} + (k_D K_D)^{-1})^{-1}$ for $k_D = \pi g a D_c$ and $K_D = \frac{\mu}{\alpha}$ as in the text, R_{jl}^{-1} can be easily approximated. Let A_{jl} be a matrix equivalent to R with the j th row and l th column removed such that $(-1)^{j+l} \det(A_{jl}) = C_{jl}$, where C is the cofactor matrix of R . Under this definition,

$$R_{jl}^{-1}(\omega) = (-1)^{j+l} \frac{\det(A_{jl})}{\det(R)}. \quad (\text{B20})$$

By the rules of determinants, any term within the determinant of R that has off-diagonal elements must have at least 2 off-diagonal elements. Since all the off-diagonal terms of R are of the form $-i\omega\Sigma(\vec{x}, \omega)$ and $\Sigma(\vec{x}, \omega)$ does not diverge as $\omega \rightarrow 0$, each of these terms must have a factor of ω that is of order 2 or higher. Thus, in the small ω limit, only the diagonal elements of R contribute to its determinant. For $j \neq l$, the creation of A_{jl} will cause two of the diagonal elements of R to be removed and $|j - l| - 1$ more to be shifted to off-diagonal elements. This will in turn cause every term in the determinant of A_{jl} to have at least one factor of the form $-i\omega\Sigma(\vec{x}, \omega)$. However, only the term with all $N - 2$ remaining factors of $\mu - i\omega(1 + \Sigma(0, \omega))$, where N is the number of cells, will have an order of ω less than 2 and will thus be the only nonnegligible term. This term will also carry a prefactor of $(-1)^{|j-l|-1}$ by the rules of determinants. With this, R_{jl}^{-1} takes the form

$$\begin{aligned} R_{jl}^{-1}(\omega) &\approx (-1)^{j+l+|j-l|-1} \frac{-i\omega\Sigma(\vec{x}_j - \vec{x}_l, \omega) (\mu - i\omega(1 + \Sigma(0, \omega)))^{N-2}}{(\mu - i\omega(1 + \Sigma(0, \omega)))^N} \\ &= \frac{i\omega\Sigma(\vec{x}_j - \vec{x}_l, \omega)}{(\mu - i\omega(1 + \Sigma(0, \omega)))^2}. \end{aligned} \quad (\text{B21})$$

Thus, R_{jl}^{-1} is seen to carry a dependence on the separation between the two cells. For $j = l$, A_{jj} is a symmetric matrix, and just like R , all of its off-diagonal components are of the form $-i\omega\Sigma(\vec{x}, \omega)$. By the same argument as that used for the determinant of R , only the diagonal terms contribute to the determinant of A_{jj} . This lets $R_{jj}^{-1}(\omega)$ to be approximated as

$$R_{jj}^{-1}(\omega) \approx (-1)^{2j} \frac{(\mu - i\omega(1 + \Sigma(0, \omega)))^{N-1}}{(\mu - i\omega(1 + \Sigma(0, \omega)))^N} = \frac{1}{\mu - i\omega(1 + \Sigma(0, \omega))}, \quad (\text{B22})$$

which is identical to R^{-1} for the $N = 1$ cell case. Thus, for long time averaging the presence of other cells does not affect any individual cell's power spectrum.

This single cell power spectrum can be computed as

$$\begin{aligned} \langle \tilde{\delta}r^*(\omega') \tilde{\delta}r(\omega) \rangle &= \frac{2\alpha\bar{c}}{\omega} (2\pi\delta(\omega - \omega')) \text{Im} \left((\mu - i\omega(1 + \Sigma(0, \omega)))^{-1} \right) \\ &= \frac{2\alpha\bar{c}}{\omega} (2\pi\delta(\omega - \omega')) \frac{\omega(1 + \text{Re}(\Sigma(0, \omega)))}{(\mu + \omega\text{Im}(\Sigma(0, \omega)))^2 + \omega^2(1 + \text{Re}(\Sigma(0, \omega)))^2} \end{aligned} \quad (\text{B23})$$

$$\begin{aligned} \Rightarrow S_r(\omega) &= \int \frac{d\omega'}{2\pi} \langle \tilde{\delta}r^*(\omega') \tilde{\delta}r(\omega) \rangle \\ &= \frac{2\alpha\bar{c}(1 + \text{Re}(\Sigma(0, \omega)))}{(\mu + \omega\text{Im}(\Sigma(0, \omega)))^2 + \omega^2(1 + \text{Re}(\Sigma(0, \omega)))^2}. \end{aligned} \quad (\text{B24})$$

To obtain the time averaged noise-to-signal ratio, the integral can be truncated at $\frac{\pi}{T}$ for $T \gg \tau_2 = \mu^{-1} + (k_D K_D)^{-1}$ as was done for ω earlier. With this, the time averaged noise-to-signal ratio in the single cell case can be approximated to be

$$\begin{aligned} \frac{C_{rT}(0)}{\bar{r}^2} &= \frac{1}{\bar{r}^2} \int_{-\frac{\pi}{T}}^{\frac{\pi}{T}} \frac{d\omega}{2\pi} S_r(\omega) \approx \frac{S_r(0)}{\bar{r}^2} \int_{-\frac{\pi}{T}}^{\frac{\pi}{T}} \frac{d\omega}{2\pi} = \frac{S_r(0)}{\bar{r}^2 T} \\ &= \frac{1}{\bar{r}^2 T} \frac{2\alpha\bar{c}(1 + \text{Re}(\Sigma(0, 0)))}{\mu^2}. \end{aligned} \quad (\text{B25})$$

Utilizing Eqs. B2 and B7 as well as setting $g = 4$ as explained in the text, Eq. B25 simplifies to

$$\begin{aligned} \frac{(\delta r)^2}{\bar{r}^2} &= \frac{C_{r_T}(0)}{\bar{r}^2} \approx \frac{1}{\bar{r}^2 T} \frac{2\alpha\bar{c} \left(1 + \frac{\alpha}{4\pi a D_c}\right)}{\mu^2} = \frac{1}{\pi a D_c T} \frac{\alpha^2 \bar{c}}{2\mu^2 \bar{r}^2} + \frac{2}{T} \frac{\alpha\bar{c}}{\mu^2 \bar{r}^2} \\ &= \frac{1}{2} \frac{1}{\pi a \bar{c} D_c T} + \frac{2}{\mu \bar{r} T}, \end{aligned} \quad (\text{B26})$$

as in the main text. Eq. B26 can be seen to be the sum of the noise the receptors inherit from the ligand diffusion, the $\frac{1}{2} \frac{1}{\pi a \bar{c} D_c T}$ term, and the noise inherent in the ligand binding-unbinding process itself, the $\frac{2}{\mu \bar{r} T}$ term.

Appendix C: Juxtacrine signaling

Now we assume that there are multiple cells in contact with each other. Each cell produces a messenger molecule species, m_j , at a rate β proportional to that cell's number of bound receptors, r_j . This species degrades at rate ν and can also be exchanged between neighboring cells at rate γ . The purpose of this section is to calculate the statistics of the long-time average of the number of messenger molecules in a particular cell.

Let \mathcal{N}_j be the set of cells neighboring the j th cell. This system can thus be modeled via

$$\frac{\partial c}{\partial t} = D_c \nabla^2 c - \sum_j \delta^3(\vec{x} - \vec{x}_j) \frac{\partial r_j}{\partial t} + \eta_c \quad (\text{C1a})$$

$$\frac{\partial r_j}{\partial t} = \alpha c(\vec{x}_j, t) - \mu r_j + \eta_{r_j} \quad (\text{C1b})$$

$$\frac{\partial m_j}{\partial t} = \beta r_j - \nu m_j + \sum_{l \in \mathcal{N}_j} \gamma (m_l - m_j) + \eta_{m_j}, \quad (\text{C1c})$$

where η_{m_j} is the noise intrinsic to the creation, degradation, and exchange of m molecules. As usual, let $m_j(t) = \bar{m}_j + \delta m_j(t)$, where \bar{m}_j is the mean value of $m_j(t)$. Eq. C1c then dictates

$$0 = \beta \bar{r}_j - \nu \bar{m}_j + \sum_{l \in \mathcal{N}_j} \gamma (\bar{m}_l - \bar{m}_j). \quad (\text{C2})$$

Assuming the binding and unbinding as well as the production and degradation parameters are the same in each cell, Eq. B2 forces $\bar{r}_j = \bar{r}_l$ for all j and l , which by Eq. C2 then forces

$$\bar{m}_j = \bar{m}_l = \frac{\beta}{\nu} \bar{r}_j \quad (\text{C3})$$

for all j and l . Additionally, Eq. C1c also dictates

$$\frac{\partial \delta m_j}{\partial t} = \beta \delta r_j - \nu \delta m_j + \sum_{l \in \mathcal{N}_j} \gamma (\delta m_l - \delta m_j) + \eta_{m_j}, \quad (\text{C4})$$

which can be Fourier transformed into

$$-i\omega \tilde{\delta m}_j = \beta \tilde{\delta r}_j - \nu \tilde{\delta m}_j + \sum_{l \in \mathcal{N}_j} \gamma (\tilde{\delta m}_l - \tilde{\delta m}_j) + \tilde{\eta}_{m_j}. \quad (\text{C5})$$

Let N_j be the number of cells neighboring the j th cell and the matrix M be defined as

$$M_{jl}(\omega) = \begin{cases} \nu + N_j \gamma - i\omega & j = l \\ -\gamma & l \in \mathcal{N}_j \\ 0 & \text{otherwise} \end{cases}. \quad (\text{C6})$$

Thus, M is seen to be a symmetric matrix. The form of M also dictates that when ω is taken to be a small parameter later, it must meet the requirement $\omega \ll \nu + \gamma$ as those are the variables ω is seen to be compared to in M . This notation allows Eq. C5 to be written as

$$\sum_l M_{jl}(\omega) \delta \tilde{m}_l = \beta \tilde{\delta} r_j + \tilde{\eta}_{mj} \implies \delta \tilde{m}_j = \sum_l M_{jl}^{-1}(\omega) \left(\beta \tilde{\delta} r_l + \tilde{\eta}_{ml} \right) \quad (\text{C7})$$

Utilizing Eq. C7 yields the cross spectrum of $m_j(t)$ and $m_l(t)$ to be

$$\begin{aligned} \langle \delta \tilde{m}_l^*(\omega') \delta \tilde{m}_j(\omega) \rangle &= \left\langle \left(\sum_u M_{lu}^{-1}(\omega') \left(\beta \tilde{\delta} r_u(\omega') + \tilde{\eta}_{mu}(\omega') \right) \right)^* \right. \\ &\quad \cdot \left. \left(\sum_s M_{js}^{-1}(\omega) \left(\beta \tilde{\delta} r_s(\omega) + \tilde{\eta}_{ms}(\omega) \right) \right) \right\rangle. \end{aligned} \quad (\text{C8})$$

At this point it is necessary to determine the properties of η_{mj} . Just as for η_{rj} , Eq. C1c is in the form of a birth-death process, which allows the power spectrum of η_{mj} to simply be written as the sum of the mean propensities. However, due to the exchange term, η_{mj} and η_{ml} cannot be independent if $l \in \mathcal{N}_j$. The cross spectrum, in this case, must be negative due to the fact that exchange means one cell is losing m molecules when the other is gaining them and must also be the sum of propensities of the exchange reaction. Thus, the power spectrum of η_{mj} takes the form

$$\begin{aligned} \langle \tilde{\eta}_{ml}^*(\omega') \tilde{\eta}_{mj}(\omega) \rangle &= \left(\beta \bar{r}_j + \nu \bar{m}_j + \sum_{s \in \mathcal{N}_j} \gamma (\bar{m}_s + \bar{m}_j) \right) \delta_{jl} (2\pi\delta(\omega - \omega')) \\ &\quad - \gamma (\bar{m}_l + \bar{m}_j) \delta_{l \in \mathcal{N}_j} (2\pi\delta(\omega - \omega')). \end{aligned} \quad (\text{C9})$$

Utilizing Eqs. C3 and C6 allows Eq. C9 to be simplified to

$$\langle \tilde{\eta}_{ml}^*(\omega') \tilde{\eta}_{mj}(\omega) \rangle = 2\bar{m} \text{Re}(M_{jl}(\omega)) (2\pi\delta(\omega - \omega')) \quad (\text{C10})$$

Since the ligand binding-unbinding process is independent of the noise in the m molecule production, any cross terms between δr_j and η_{ml} must vanish. This allows Eq. C8 to be written as

$$\begin{aligned} \langle \delta \tilde{m}_l^*(\omega') \delta \tilde{m}_j(\omega) \rangle &= \sum_{s,u} M_{js}^{-1}(\omega) (M_{lu}^{-1}(\omega'))^* \left(\beta^2 \langle \tilde{\delta} r_u^*(\omega') \tilde{\delta} r_s(\omega) \rangle + \langle \tilde{\eta}_{ms}^*(\omega') \tilde{\eta}_{mu}(\omega) \rangle \right) \\ &= 2(2\pi\delta(\omega - \omega')) \sum_{s,u} M_{js}^{-1}(\omega) (M_{lu}^{-1}(\omega))^{*} \left(\beta^2 \frac{\alpha \bar{c}}{\omega} \text{Im}(R_{su}^{-1}(\omega)) + \bar{m} \text{Re}((M_{su}(\omega))^*) \right), \end{aligned} \quad (\text{C11})$$

where Eq. B19 has been used, $\text{Re}(M_{su}(\omega))$ from Eq. C10 has been freely changed to $\text{Re}((M_{su}(\omega))^*)$, and all instances of ω' outside the δ function were freely replaced with ω due to the δ function being a global factor.

In order to simplify Eq. C11, first let a and b be two arbitrary complex numbers. The product $a \text{Re}(b)$ can be reordered as

$$\begin{aligned} a \text{Re}(b) &= \text{Re}(a) \text{Re}(b) + i \text{Im}(a) \text{Re}(b) \\ &= (\text{Re}(a) \text{Re}(b) - \text{Im}(a) \text{Im}(b)) + \text{Im}(a) (\text{Im}(b) + i \text{Re}(b)) \\ &= \text{Re}(ab) + ib^* \text{Im}(a) = \text{Re}(ab) - ib^* \text{Im}(a^*) \end{aligned} \quad (\text{C12})$$

Temporarily ignoring the R_{su}^{-1} term and applying Eq. C12 to the $(M_{lu}^{-1}(\omega))^* \text{Re}((M_{su}(\omega))^*)$ term in Eq. C11 yields

$$\begin{aligned} &\sum_{s,u} M_{js}^{-1}(\omega) (M_{lu}^{-1}(\omega))^* \text{Re}((M_{su}(\omega))^*) \\ &= \sum_{s,u} M_{js}^{-1}(\omega) \left(\text{Re}((M_{lu}^{-1}(\omega) M_{su}(\omega))^*) - i M_{su}(\omega) \text{Im}(M_{lu}^{-1}(\omega)) \right). \end{aligned} \quad (\text{C13})$$

Separating out the sums and freely changing $\text{Re}((M_{lu}^{-1}(\omega) M_{su}(\omega))^*)$ to $\text{Re}(M_{lu}^{-1}(\omega) M_{su}(\omega))$ then yields

$$\begin{aligned} &\sum_{s,u} M_{js}^{-1}(\omega) (M_{lu}^{-1}(\omega))^* \text{Re}((M_{su}(\omega))^*) \\ &= \sum_s M_{js}^{-1}(\omega) \sum_u \text{Re}(M_{lu}^{-1}(\omega) M_{su}(\omega)) - i \sum_u \text{Im}(M_{lu}^{-1}(\omega)) \sum_s M_{js}^{-1}(\omega) M_{su}(\omega). \end{aligned} \quad (\text{C14})$$

Since M is symmetric, $M_{su}(\omega)$ in the first term can be freely changed to $M_{us}(\omega)$. This implies that when the summation over u is brought inside the Re operator, $M_{lu}^{-1}(\omega) M_{su}(\omega)$ will collapse to δ_{ls} , which has no imaginary part. Thus, the entire summation simplifies to δ_{ls} . Similarly, the summation over s in the second term will collapse into δ_{ju} . These along with once again using the symmetry of M to freely change $M_{lu}^{-1}(\omega)$ to $M_{ul}^{-1}(\omega)$ in the second term then yields

$$\begin{aligned} \sum_{s,u} M_{js}^{-1}(\omega) (M_{lu}^{-1}(\omega))^* \text{Re}((M_{su}(\omega))^*) &= \sum_s M_{js}^{-1}(\omega) \delta_{ls} - i \sum_u \text{Im}(M_{ul}^{-1}(\omega)) \delta_{ju} \\ &= M_{jl}^{-1}(\omega) - i \text{Im}(M_{jl}^{-1}(\omega)) = \text{Re}(M_{jl}^{-1}(\omega)). \end{aligned} \quad (\text{C15})$$

Applying Eq. C15 to Eq. C11 then yields

$$\begin{aligned} &\langle \tilde{m}_l^*(\omega') \tilde{m}_j(\omega) \rangle \\ &= 2(2\pi\delta(\omega - \omega')) \left(\bar{m} \text{Re}(M_{jl}^{-1}(\omega)) + \frac{\alpha\beta^2\bar{c}}{\omega} \sum_{s,u} M_{js}^{-1}(\omega) (M_{lu}^{-1}(\omega))^* \text{Im}(R_{su}^{-1}(\omega)) \right). \end{aligned} \quad (\text{C16})$$

From here, a few properties of M can be used to simplify Eq. C16 in particular limits of γ or N . First, for $\gamma \ll \nu$, M approximately becomes $(\nu - i\omega) I_N$, where I_N is the identity matrix of rank N . This makes inverting M trivial and reduces Eq. C16 to

$$\begin{aligned} &\langle \tilde{m}_l^*(\omega') \tilde{m}_j(\omega) \rangle \\ &= 2(2\pi\delta(\omega - \omega')) \left(\bar{m} \text{Re}\left(\frac{\delta_{jl}}{\nu - i\omega}\right) + \frac{\alpha\beta^2\bar{c}}{\omega} \left| \frac{1}{\nu - i\omega} \right|^2 \text{Im}(R_{jl}^{-1}(\omega)) \right). \end{aligned} \quad (\text{C17})$$

Utilizing the relations between \bar{m} and \bar{r} in Eq. C3 and caculating the time averaged noise-to-signal ratio of $m_j(t)$ in the same manner as was done for Eq. B25 (this time with the additional assumption $T \gg \tau_3 = (\mu + \gamma)^{-1}$ as outlined by the requirement for ω to be considered small) yields

$$\begin{aligned} \lim_{\gamma \rightarrow 0} \frac{(\delta m)^2}{\bar{m}^2} &= \frac{S_m(0)}{\bar{m}^2 T} = \frac{1}{\bar{m}^2 T} \int \frac{d\omega'}{2\pi} \langle \tilde{m}_j^*(\omega') \tilde{m}_j(0) \rangle \\ &= \frac{2}{\nu \bar{m} T} + \frac{2\alpha\bar{c}}{\bar{r}^2 T} \lim_{\omega \rightarrow 0} \frac{1}{\omega} \text{Im}(R_{jj}^{-1}(\omega)) \end{aligned} \quad (\text{C18})$$

When Eq. B22 is used to input the form of $R_{jj}^{-1}(\omega)$, Eq. C18 simplifies to Eq. B26 with the addition of the $\frac{2}{\nu \bar{m} T}$ term from the noise inherent in the production and degradation of m .

Second, for $\gamma \gg \nu$ the cells are effectively communicating at infinite speed. Physically, this implies that every cell in the cluster communicates with every other cell equally, which mathematically translates to the dictation that M_{jl}^{-1} must be independent of j and l . Let \vec{X} be a column vector with unit entries. By Eq. C6 it is easy to see that

$$M\vec{X} = (\nu - i\omega)\vec{X}. \quad (\text{C19})$$

Thus, \vec{X} is an eigenvector of M , which in turn implies it must also be an eigenvector of M^{-1} satisfying

$$M^{-1}\vec{X} = (\nu - i\omega)^{-1}\vec{X}. \quad (\text{C20})$$

Since M_{jl}^{-1} must be independent of j and l , the only way Eq. C20 can be true is if

$$\lim_{\gamma \rightarrow \infty} M_{jl}^{-1} = \frac{1}{N(\nu - i\omega)}. \quad (\text{C21})$$

This allows Eq. C16 to reduce to

$$\begin{aligned} &\langle \tilde{m}_l^*(\omega') \tilde{m}_j(\omega) \rangle \\ &= 2(2\pi\delta(\omega - \omega')) \left(\frac{\bar{m}}{N} \text{Re}\left(\frac{1}{\nu - i\omega}\right) + \frac{\alpha\beta^2\bar{c}}{N^2\omega|\nu - i\omega|^2} \sum_{s,u} \text{Im}(R_{su}^{-1}(\omega)) \right). \end{aligned} \quad (\text{C22})$$

Once again calculating the noise-to-signal ratio (again requiring $T \gg \tau_3$) yields

$$\begin{aligned} \lim_{\gamma \rightarrow \infty} \frac{(\delta m)^2}{\bar{m}^2} &= \frac{S_m(0)}{\bar{m}^2 T} = \frac{1}{\bar{m}^2 T} \int \frac{d\omega'}{2\pi} \langle \delta \tilde{m}_j^*(\omega') \delta \tilde{m}_j(0) \rangle \\ &= \frac{2}{\nu \bar{m} T N} + \frac{2\alpha \bar{c}}{\bar{r}^2 N^2 T} \sum_{s,u} \lim_{\omega \rightarrow 0} \frac{1}{\omega} \text{Im}(R_{su}^{-1}(\omega)) \end{aligned} \quad (\text{C23})$$

Finally, Eq. C16 can be easily represented under no assumptions about γ but for the limiting case of $N = 2$ cells. When the cells are adjacent to each other, M and M^{-1} take the form

$$M = \begin{bmatrix} \nu + \gamma - i\omega & -\gamma \\ -\gamma & \nu + \gamma - i\omega \end{bmatrix} \quad (\text{C24a})$$

$$M^{-1} = \frac{1}{(\nu - i\omega)(\nu - i\omega + 2\gamma)} \begin{bmatrix} \nu + \gamma - i\omega & \gamma \\ \gamma & \nu + \gamma - i\omega \end{bmatrix}. \quad (\text{C24b})$$

Let $\vec{\ell} = \vec{x}_1 - \vec{x}_2$ and ω be taken to 0. With these and Eqs. B21 and B22, the time averaged noise-to-signal ratio of $m_1(t)$ can be calculated in the same way as was done for Eq. B25 (still requiring $T \gg \tau_3$) to yield

$$\begin{aligned} \frac{(\delta m)^2}{\bar{m}^2} &= \frac{S_1(0)}{\bar{m}^2 T} = \frac{1}{\bar{m}^2 T} \int \frac{d\omega'}{2\pi} \langle \delta \tilde{m}_1^*(\omega') \delta \tilde{m}_1(0) \rangle \\ &= \frac{1}{\bar{m}^2 T} \left(2\bar{m} \text{Re}(M_{11}^{-1}(0)) + 2\alpha\beta^2\bar{c} \sum_{s,u} M_{js}^{-1}(0) (M_{lu}^{-1}(0))^* \lim_{\omega \rightarrow 0} \frac{1}{\omega} \text{Im}(R_{su}^{-1}(\omega)) \right) \\ &= \frac{1}{\bar{m}^2 T} \left(2\bar{m} \frac{\nu + \gamma}{\nu(\nu + 2\gamma)} + 2\alpha\beta^2\bar{c} \left(2 \frac{\nu + \gamma}{\nu(\nu + 2\gamma)} \frac{\gamma}{\nu(\nu + 2\gamma)} \frac{\text{Re}(\Sigma(\vec{\ell}, 0))}{\mu^2} \right. \right. \\ &\quad \left. \left. + \left(\left(\frac{\nu + \gamma}{\nu(\nu + 2\gamma)} \right)^2 + \left(\frac{\gamma}{\nu(\nu + 2\gamma)} \right)^2 \right) \frac{1 + \text{Re}(\Sigma(0, 0))}{\mu^2} \right) \right). \end{aligned} \quad (\text{C25})$$

Utilizing the relations between \bar{m} , \bar{r} , and \bar{c} in Eqs. B2 and C3 as well as the explicit form of $\Sigma(\vec{x}, 0)$ in Eqs. B6 and B7 allows Eq. C25 to be simplified to

$$\frac{(\delta m)^2}{\bar{m}^2} = \frac{1}{\pi a \bar{c} D_c T} \frac{\nu^2 + 3\nu\gamma + 3\gamma^2}{2(\nu + 2\gamma)^2} + \frac{1}{\mu \bar{r} T} \frac{2(\nu^2 + 2\nu\gamma + 2\gamma^2)}{(\nu + 2\gamma)^2} + \frac{1}{\nu \bar{m} T} \frac{2(\nu + \gamma)}{\nu + 2\gamma}, \quad (\text{C26})$$

where $|\vec{\ell}|$ has been set to be exactly $2a$ to reflect the necessity of the cells to be adjacent to each other in order to exchange m molecules. Eq. C26 can be seen to be easily separable into the three distinct terms which reflect the noise inherited from the ligand diffusion, binding-unbinding process, and m birth-death and exchange processes. Of important note is that under the $\gamma \ll \nu$ limit Eq. C26 reduces to Eq. B26 plus the term $\frac{2}{\nu \bar{m} T}$. Conversely, under the $\gamma \gg \nu$ limit (which is equivalent to $\lambda = 2a\sqrt{\frac{\gamma}{\nu}} \gg a$) the second fraction of each term go to $\frac{3}{8}$, 1, and 1 respectively. The first term, which is the extrinsic noise, is reproduced in the main text.

Appendix D: Autocrine signaling

We here assume that the cells produce a messenger molecule with the same production and degradation rate as in the previous section, but instead of being exchanged between neighboring cells they are secreted into the environment and diffuse with a diffusion constant of D_ρ . The purpose of this section is to calculate the statistics of the long-time average of the number of messenger molecules within the volume of a particular cell.

This system can be modeled via

$$\frac{\partial c}{\partial t} = D_c \nabla^2 c - \sum_j \delta^3(\vec{x} - \vec{x}_j) \frac{\partial r_j}{\partial t} + \eta_c \quad (\text{D1a})$$

$$\frac{\partial r_j}{\partial t} = \alpha c(\vec{x}_j, t) - \mu r_j + \eta_{rj} \quad (\text{D1b})$$

$$\frac{\partial \rho}{\partial t} = D_\rho \nabla^2 \rho - \nu \rho + \sum_j \delta^3(\vec{x} - \vec{x}_j) (\beta r_j + \eta_{pj}) + \eta_d, \quad (\text{D1c})$$

where $\rho(\vec{x}, t)$ is the density field of the diffusing messenger molecule and η_{pj} and η_d are the production from the j th cell, and the degradation and diffusive noise terms, respectively. Again, let $\rho(\vec{x}, t) = \bar{\rho}(\vec{x}) + \delta\rho(\vec{x}, t)$, where $\bar{\rho}(\vec{x})$ is the mean value of $\rho(\vec{x}, t)$ as a function of space. Since ρ is being produced at each cell and allowed to diffuse, $\bar{\rho}(\vec{x})$ cannot be constant in space and by Eq. D1c must obey

$$0 = D_\rho \nabla^2 \bar{\rho} - \nu \bar{\rho} + \sum_j \delta^3(\vec{x} - \vec{x}_j) \beta \bar{r}_j, \quad (\text{D2})$$

which is solved by

$$\bar{\rho}(\vec{x}) = \frac{1}{4\pi D_\rho} \sum_j \frac{\beta \bar{r}_j}{|\vec{x} - \vec{x}_j|} e^{-|\vec{x} - \vec{x}_j| \sqrt{\frac{\nu}{D_\rho}}}. \quad (\text{D3})$$

Additionally, Eq. D1c also dictates

$$\frac{\partial \delta\rho}{\partial t} = D_\rho \nabla^2 \delta\rho - \nu \delta\rho + \sum_j \delta^3(\vec{x} - \vec{x}_j) (\beta \delta r_j + \eta_{pj}) + \eta_d, \quad (\text{D4})$$

which can be Fourier transformed into

$$\begin{aligned} -i\omega \tilde{\delta\rho} &= -D_\rho k^2 \tilde{\delta\rho} - \nu \tilde{\delta\rho} + \sum_j e^{i\vec{k} \cdot (\vec{x} - \vec{x}_j)} (\beta \tilde{\delta r}_j + \tilde{\eta}_{pj}) + \tilde{\eta}_d \\ \implies \tilde{\delta\rho} &= \frac{\sum_j e^{i\vec{k} \cdot \vec{x}_j} (\beta \tilde{\delta r}_j + \tilde{\eta}_{pj}) + \tilde{\eta}_d}{\nu + D_\rho k^2 - i\omega}. \end{aligned} \quad (\text{D5})$$

Since the noise in each r_j is independent of the noise in the production and degradation/diffusion of ρ , and the production and diffusion noises must be independent of each other, the cross spectrum of $\rho(\vec{x}, t)$ can be written as

$$\begin{aligned} \langle \tilde{\delta\rho}^*(\vec{k}', \omega') \tilde{\delta\rho}(\vec{k}, \omega) \rangle &= \left\langle \left(\frac{\sum_l e^{i\vec{k}' \cdot \vec{x}_l} (\beta \tilde{\delta r}_l(\omega') + \tilde{\eta}_{pl}(\omega')) + \tilde{\eta}_d(\vec{k}', \omega')}{\nu + D_\rho k'^2 - i\omega'} \right)^* \right. \\ &\quad \cdot \left. \left(\frac{\sum_j e^{i\vec{k} \cdot \vec{x}_j} (\beta \tilde{\delta r}_j(\omega) + \tilde{\eta}_{pj}(\omega)) + \tilde{\eta}_d(\vec{k}, \omega)}{\nu + D_\rho k^2 - i\omega} \right) \right\rangle \\ &= \frac{\sum_{j,l} e^{i(\vec{k} \cdot \vec{x}_j - \vec{k}' \cdot \vec{x}_l)} (\beta^2 \langle \tilde{\delta r}_l^*(\omega') \tilde{\delta r}_j(\omega) \rangle + \langle \tilde{\eta}_{pl}^*(\omega') \tilde{\eta}_{pj}(\omega) \rangle) + \langle \tilde{\eta}_d^*(\vec{k}', \omega') \tilde{\eta}_d(\vec{k}, \omega) \rangle}{(\nu + D_\rho k^2 - i\omega)(\nu + D_\rho k'^2 + i\omega')}. \end{aligned} \quad (\text{D6})$$

From here the spectra of both η_{pj} and η_d are needed. Since η_d is also a diffusive noise term, it must follow the same formalism used in Eq. A10. However, unlike c , ρ can degrade, meaning a degradation term must be added to the noise. This yields

$$\langle \eta_d(\vec{x}', t') \eta_d(\vec{x}, t) \rangle = 2D_\rho \delta(t - t') \vec{\nabla}_x \cdot \vec{\nabla}_{x'} (\bar{\rho}(\vec{x}) \delta^3(\vec{x} - \vec{x}')) + \nu \bar{\rho}(\vec{x}) \delta(t - t') \delta^3(\vec{x} - \vec{x}'). \quad (\text{D7})$$

Eq. D7 can then be Fourier transformed to yield

$$\begin{aligned} \langle \tilde{\eta}_d^*(\vec{k}', \omega') \tilde{\eta}_d(\vec{k}, \omega) \rangle &= \int d^3x d^3x' dt dt' \langle \eta_d(\vec{x}', t') \eta_d(\vec{x}, t) \rangle (e^{i\vec{k} \cdot \vec{x}} e^{i\omega t}) (e^{i\vec{k}' \cdot \vec{x}'} e^{i\omega' t'})^* \\ &= 2D_\rho \int d^3x d^3x' dt dt' e^{i(\vec{k} \cdot \vec{x} - \vec{k}' \cdot \vec{x}')} e^{i(\omega t - \omega' t')} \delta(t - t') \vec{\nabla}_x \cdot \vec{\nabla}_{x'} (\bar{\rho}(\vec{x}) \delta^3(\vec{x} - \vec{x}')) \\ &\quad + \nu \int d^3x d^3x' dt dt' e^{i(\vec{k} \cdot \vec{x} - \vec{k}' \cdot \vec{x}')} e^{i(\omega t - \omega' t')} \bar{\rho}(\vec{x}) \delta(t - t') \delta^3(\vec{x} - \vec{x}'). \end{aligned} \quad (\text{D8})$$

The δ function makes the t' integrals trivial, which leaves the only time dependent term in the integrands as $e^{it(\omega-\omega')}$. Eq. A12 can then be used to solve the t integral and transform $\delta^3(\vec{x}-\vec{x}')$ into an integral form in the first integral. In the second integral, the δ^3 function makes the x' integral trivial. Combining these with Eq. D3 allows Eq. D8 to be written as

$$\begin{aligned} \langle \tilde{\eta}_d^* (\vec{k}', \omega') \tilde{\eta}_d (\vec{k}, \omega) \rangle &= \frac{1}{2\pi} (2\pi\delta(\omega-\omega')) \int d^3x d^3x' e^{i(\vec{k}\cdot\vec{x}-\vec{k}'\cdot\vec{x}')} \\ &\cdot \vec{\nabla}_x \cdot \vec{\nabla}_{x'} \left(\left(\sum_j \frac{\beta \bar{r}_j}{|\vec{x}-\vec{x}_j|} e^{-|\vec{x}-\vec{x}_j|\sqrt{\frac{\nu}{D_\rho}}} \right) \left(\int \frac{d^3\kappa}{(2\pi)^3} e^{i\vec{\kappa}\cdot(\vec{x}-\vec{x}')} \right) \right) \\ &+ \frac{\nu}{4\pi D_\rho} (2\pi\delta(\omega-\omega')) \int d^3x e^{i\vec{x}\cdot(\vec{k}-\vec{k}')} \sum_j \frac{\beta \bar{r}_j}{|\vec{x}-\vec{x}_j|} e^{-|\vec{x}-\vec{x}_j|\sqrt{\frac{\nu}{D_\rho}}}. \end{aligned} \quad (D9)$$

Focusing on the first integral, moving the κ integral outside the gradient operators before applying them then yields

$$\begin{aligned} \langle \tilde{\eta}_d^* (\vec{k}', \omega') \tilde{\eta}_d (\vec{k}, \omega) \rangle &= \frac{1}{(2\pi)^4} (2\pi\delta(\omega-\omega')) \int d^3x d^3x' d^3\kappa e^{i(\vec{k}\cdot\vec{x}-\vec{k}'\cdot\vec{x}')} (-i\vec{\kappa}) \\ &\cdot \left(i\vec{\kappa} e^{i\vec{\kappa}\cdot(\vec{x}-\vec{x}')} \sum_j \frac{\beta \bar{r}_j}{|\vec{x}-\vec{x}_j|} e^{-|\vec{x}-\vec{x}_j|\sqrt{\frac{\nu}{D_\rho}}} + e^{i\vec{\kappa}\cdot(\vec{x}-\vec{x}')} \sum_j \vec{\nabla}_x \frac{\beta \bar{r}_j}{|\vec{x}-\vec{x}_j|} e^{-|\vec{x}-\vec{x}_j|\sqrt{\frac{\nu}{D_\rho}}} \right) \\ &+ \frac{\nu}{4\pi D_\rho} (2\pi\delta(\omega-\omega')) \int d^3x e^{i\vec{x}\cdot(\vec{k}-\vec{k}')} \sum_j \frac{\beta \bar{r}_j}{|\vec{x}-\vec{x}_j|} e^{-|\vec{x}-\vec{x}_j|\sqrt{\frac{\nu}{D_\rho}}} \\ &= \frac{1}{(2\pi)^4} (2\pi\delta(\omega-\omega')) \int d^3x d^3x' d^3\kappa e^{i\vec{x}\cdot(\vec{k}+\vec{\kappa})} e^{-i\vec{x}'\cdot(\vec{k}'+\vec{\kappa})} \\ &\cdot \sum_j \left(\kappa^2 \frac{\beta \bar{r}_j}{|\vec{x}-\vec{x}_j|} e^{-|\vec{x}-\vec{x}_j|\sqrt{\frac{\nu}{D_\rho}}} - i\vec{\kappa} \cdot \vec{\nabla}_x \frac{\beta \bar{r}_j}{|\vec{x}-\vec{x}_j|} e^{-|\vec{x}-\vec{x}_j|\sqrt{\frac{\nu}{D_\rho}}} \right) \\ &+ \frac{\nu}{4\pi D_\rho} (2\pi\delta(\omega-\omega')) \int d^3x e^{i\vec{x}\cdot(\vec{k}-\vec{k}')} \sum_j \frac{\beta \bar{r}_j}{|\vec{x}-\vec{x}_j|} e^{-|\vec{x}-\vec{x}_j|\sqrt{\frac{\nu}{D_\rho}}}. \end{aligned} \quad (D10)$$

Since x' only appears in the term $e^{-i\vec{x}'\cdot(\vec{k}'+\vec{\kappa})}$, Eq. A12 can again be used to solve the x' integral, which will then make the κ integral trivial due to the resultant δ function. This causes Eq. D10 to simplify to

$$\begin{aligned} \langle \tilde{\eta}_d^* (\vec{k}', \omega') \tilde{\eta}_d (\vec{k}, \omega) \rangle &= \frac{1}{2\pi} (2\pi\delta(\omega-\omega')) \int d^3x d^3\kappa e^{i\vec{x}\cdot(\vec{k}+\vec{\kappa})} \delta^3(\vec{k}'+\vec{\kappa}) \\ &\cdot \sum_j \left(\kappa^2 \frac{\beta \bar{r}_j}{|\vec{x}-\vec{x}_j|} e^{-|\vec{x}-\vec{x}_j|\sqrt{\frac{\nu}{D_\rho}}} - i\vec{\kappa} \cdot \vec{\nabla}_x \frac{\beta \bar{r}_j}{|\vec{x}-\vec{x}_j|} e^{-|\vec{x}-\vec{x}_j|\sqrt{\frac{\nu}{D_\rho}}} \right) \\ &+ \frac{\nu}{4\pi D_\rho} (2\pi\delta(\omega-\omega')) \int d^3x e^{i\vec{x}\cdot(\vec{k}-\vec{k}')} \sum_j \frac{\beta \bar{r}_j}{|\vec{x}-\vec{x}_j|} e^{-|\vec{x}-\vec{x}_j|\sqrt{\frac{\nu}{D_\rho}}} \\ &= \frac{1}{2\pi} (2\pi\delta(\omega-\omega')) \int d^3x e^{i\vec{x}\cdot(\vec{k}-\vec{k}')} \\ &\cdot \sum_j \beta \bar{r}_j \left(k'^2 \frac{1}{|\vec{x}-\vec{x}_j|} e^{-|\vec{x}-\vec{x}_j|\sqrt{\frac{\nu}{D_\rho}}} + i\vec{k}' \cdot \vec{\nabla}_x \frac{1}{|\vec{x}-\vec{x}_j|} e^{-|\vec{x}-\vec{x}_j|\sqrt{\frac{\nu}{D_\rho}}} \right) \\ &+ \frac{\nu}{4\pi D_\rho} (2\pi\delta(\omega-\omega')) \int d^3x e^{i\vec{x}\cdot(\vec{k}-\vec{k}')} \sum_j \frac{\beta \bar{r}_j}{|\vec{x}-\vec{x}_j|} e^{-|\vec{x}-\vec{x}_j|\sqrt{\frac{\nu}{D_\rho}}}. \end{aligned} \quad (D11)$$

Let $\vec{v}_j = \vec{x} - \vec{x}_j$ in both integrals. Since the x integral is over all of x -space, this transformation does not change the limits of integration. Additionally, $d^3x = d^3v_j$ and $\vec{\nabla}_x = \vec{\nabla}_{v_j}$ due to x and v_j being related by a simple translation.

Utilizing this and moving the summations in Eq. D11 outside the integrals allows it to be written as

$$\begin{aligned} \langle \tilde{\eta}_d^* (\vec{k}', \omega') \tilde{\eta}_d (\vec{k}, \omega) \rangle &= \frac{1}{2\pi} (2\pi\delta(\omega - \omega')) \sum_j \beta \bar{r}_j e^{i\vec{x}_j \cdot (\vec{k} - \vec{k}')} \int d^3 v_j e^{i\vec{v}_j \cdot (\vec{k} - \vec{k}')} \\ &\cdot \left(k'^2 \frac{1}{v_j} e^{-v_j \sqrt{\frac{\nu}{D_\rho}}} + i\vec{k}' \cdot \vec{\nabla}_{v_j} \frac{1}{v_j} e^{-v_j \sqrt{\frac{\nu}{D_\rho}}} \right) \\ &+ \frac{\nu}{4\pi D_\rho} (2\pi\delta(\omega - \omega')) \sum_j \beta \bar{r}_j e^{i\vec{x}_j \cdot (\vec{k} - \vec{k}')} \int d^3 v_j \frac{1}{v_j} e^{-v_j \sqrt{\frac{\nu}{D_\rho}}} e^{i\vec{v}_j \cdot (\vec{k} - \vec{k}')} . \end{aligned} \quad (D12)$$

Since $\frac{1}{|\vec{v}_j|} e^{-|\vec{v}_j| \sqrt{\frac{\nu}{D_\rho}}}$ goes to 0 exponentially as $|\vec{v}_j| \rightarrow \infty$, the second term in the first integral of Eq. D12 can be integrated by parts with the net result of simply adding a factor of -1 and moving the gradient to apply to $e^{i\vec{v}_j \cdot (\vec{k} - \vec{k}')}$. This causes Eq. D12 to simplify to

$$\begin{aligned} \langle \tilde{\eta}_d^* (\vec{k}', \omega') \tilde{\eta}_d (\vec{k}, \omega) \rangle &= \frac{1}{2\pi} (2\pi\delta(\omega - \omega')) \sum_j \beta \bar{r}_j e^{i\vec{x}_j \cdot (\vec{k} - \vec{k}')} \\ &\cdot \int d^3 v_j \frac{1}{v_j} e^{-v_j \sqrt{\frac{\nu}{D_\rho}}} \left(k'^2 e^{i\vec{v}_j \cdot (\vec{k} - \vec{k}')} - i\vec{k}' \cdot \vec{\nabla}_{v_j} e^{i\vec{v}_j \cdot (\vec{k} - \vec{k}')} \right) \\ &+ \frac{\nu}{4\pi D_\rho} (2\pi\delta(\omega - \omega')) \sum_j \beta \bar{r}_j e^{i\vec{x}_j \cdot (\vec{k} - \vec{k}')} \int d^3 v_j \frac{1}{v_j} e^{-v_j \sqrt{\frac{\nu}{D_\rho}}} e^{i\vec{v}_j \cdot (\vec{k} - \vec{k}')} \\ &= \frac{1}{2\pi} (2\pi\delta(\omega - \omega')) \sum_j \beta \bar{r}_j e^{i\vec{x}_j \cdot (\vec{k} - \vec{k}')} \int d^3 v_j \frac{\vec{k} \cdot \vec{k}'}{v_j} e^{-v_j \sqrt{\frac{\nu}{D_\rho}}} e^{i\vec{v}_j \cdot (\vec{k} - \vec{k}')} \\ &+ \frac{\nu}{4\pi D_\rho} (2\pi\delta(\omega - \omega')) \sum_j \beta \bar{r}_j e^{i\vec{x}_j \cdot (\vec{k} - \vec{k}')} \int d^3 v_j \frac{1}{v_j} e^{-v_j \sqrt{\frac{\nu}{D_\rho}}} e^{i\vec{v}_j \cdot (\vec{k} - \vec{k}')} . \end{aligned} \quad (D13)$$

The integrals in Eq. D13 can be solved via the known Fourier transformation

$$\int d^3 z \frac{1}{z} e^{-z l} e^{i\vec{z} \cdot \vec{\kappa}} = \frac{4\pi}{l^2 + \kappa^2} . \quad (D14)$$

Letting $\vec{z} = \vec{v}_j$, $l = \sqrt{\frac{\nu}{D_\rho}}$ and $\vec{\kappa} = \vec{k} - \vec{k}'$, substituting Eq. D14 into Eq. D13 yields

$$\langle \tilde{\eta}_d^* (\vec{k}', \omega') \tilde{\eta}_d (\vec{k}, \omega) \rangle = (2\pi\delta(\omega - \omega')) \frac{2D_\rho \vec{k} \cdot \vec{k}' + \nu}{\nu + D_\rho |\vec{k} - \vec{k}'|^2} \sum_j \beta \bar{r}_j e^{i\vec{x}_j \cdot (\vec{k} - \vec{k}')} . \quad (D15)$$

Returning to η_{pj} , since each cell produces ρ independently of each other cell, the production noises must be independent. Additionally, since the production is a birth only process, its power spectrum must simply be the mean propensity of the production, which in turn yields

$$\langle \tilde{\eta}_{pl}^* (\omega') \tilde{\eta}_{pj} (\omega) \rangle = \beta \bar{r}_j \delta_{jl} (2\pi\delta(\omega - \omega')) \quad (D16)$$

Substituting Eqs. B19, D15, and D16 into Eq. D6 then yields

$$\begin{aligned} \langle \tilde{\delta\rho}^* (\vec{k}', \omega') \tilde{\delta\rho} (\vec{k}, \omega) \rangle &= \frac{2\pi\delta(\omega - \omega')}{(\nu + D_\rho k^2 - i\omega)(\nu + D_\rho k'^2 + i\omega')} \\ &\cdot \left(\sum_{j,l} e^{i(\vec{k} \cdot \vec{x}_j - \vec{k}' \cdot \vec{x}_l)} \left(\beta^2 \frac{2\alpha\bar{c}}{\omega} \text{Im} (R_{jl}^{-1}(\omega)) + \beta \bar{r}_j \delta_{jl} \right) + \frac{2D_\rho \vec{k} \cdot \vec{k}' + \nu}{\nu + D_\rho |\vec{k} - \vec{k}'|^2} \sum_j \beta \bar{r}_j e^{i\vec{x}_j \cdot (\vec{k} - \vec{k}')} \right) \\ &= \frac{2\pi\delta(\omega - \omega')}{(\nu + D_\rho k^2 - i\omega)(\nu + D_\rho k'^2 + i\omega')} \left(\sum_{j,l} \frac{2\alpha\beta^2\bar{c}}{\omega} e^{i(\vec{k} \cdot \vec{x}_j - \vec{k}' \cdot \vec{x}_l)} \text{Im} (R_{jl}^{-1}(\omega)) \right. \\ &\quad \left. + \left(1 + \frac{2D_\rho \vec{k} \cdot \vec{k}' + \nu}{\nu + D_\rho |\vec{k} - \vec{k}'|^2} \right) \sum_j \beta \bar{r}_j e^{i\vec{x}_j \cdot (\vec{k} - \vec{k}')} \right) , \end{aligned} \quad (D17)$$

where all instances of ω' outside the δ function have been freely replaced with ω due to the δ function being a global factor.

Now, let $m_j(t)$ be the number of ρ molecules in the j th cell, which has volume V_j and radius a . $m_j(t)$ can be calculated from $\rho(\vec{x}, t)$ via

$$m_j(t) = \int_{V_j} d^3x \rho(\vec{x}, t). \quad (\text{D18})$$

Once again, let $m_j(t) = \bar{m}_j + \delta m_j(t)$, where \bar{m}_j is the mean value of $m_j(t)$. Since $\bar{\rho}(\vec{x})$ is the mean value of $\rho(\vec{x}, t)$, this implies

$$\bar{m}_j = \int_{V_j} d^3x \bar{\rho}(\vec{x}) \implies \delta m_j(t) = \int_{V_j} d^3x \delta \rho(\vec{x}, t). \quad (\text{D19})$$

Fourier transforming the second part of Eq. D19 then yields

$$\delta \tilde{m}_j(\omega) = \int_{V_j} d^3x \int \frac{d^3k}{(2\pi)^3} \delta \rho(\vec{k}, \omega) e^{-i\vec{k} \cdot \vec{x}}. \quad (\text{D20})$$

With this, the cross spectrum of $m_j(t)$ can be calculated to be

$$\begin{aligned} \langle \delta \tilde{m}_j^*(\omega') \delta \tilde{m}_j(\omega) \rangle &= \left\langle \left(\int_{V_j} d^3x' \int \frac{d^3k'}{(2\pi)^3} \delta \rho^*(\vec{k}', \omega') e^{i\vec{k}' \cdot \vec{x}'} \right) \left(\int_{V_j} d^3x \int \frac{d^3k}{(2\pi)^3} \delta \rho(\vec{k}, \omega) e^{-i\vec{k} \cdot \vec{x}} \right) \right\rangle \\ &= \frac{1}{(2\pi)^6} \int_{V_j} d^3x d^3x' \int d^3k d^3k' \langle \delta \rho^*(\vec{k}', \omega') \delta \rho(\vec{k}, \omega) \rangle e^{i(\vec{k}' \cdot \vec{x}' - \vec{k} \cdot \vec{x})}. \end{aligned} \quad (\text{D21})$$

Again, let $\vec{v}_j = \vec{x} - \vec{x}_j$ and $\vec{v}'_j = \vec{x}' - \vec{x}_j$ and V be the volume of the cell centered at the origin. This, along with Eq. D17, transforms Eq. D21 into

$$\begin{aligned} &\langle \delta \tilde{m}_j^*(\omega') \delta \tilde{m}_j(\omega) \rangle \\ &= \frac{1}{(2\pi)^6} \int_V d^3v_j d^3v'_j \int d^3k d^3k' \langle \delta \rho^*(\vec{k}', \omega') \delta \rho(\vec{k}, \omega) \rangle e^{i(\vec{k}' \cdot \vec{v}'_j - \vec{k} \cdot \vec{v}_j)} e^{i\vec{x}_j \cdot (\vec{k}' - \vec{k})} \\ &= 2\pi \delta(\omega - \omega') (I_1(\omega) + I_2(\omega) + I_3(\omega) + I_4(\omega)), \end{aligned} \quad (\text{D22})$$

where

$$\begin{aligned} I_1(\omega) &= \frac{1}{(2\pi)^6} \int_V d^3v_j d^3v'_j \int d^3k d^3k' \frac{1}{(\nu + D_\rho k^2 - i\omega)(\nu + D_\rho k'^2 + i\omega)} \\ &\quad \cdot e^{i(\vec{k}' \cdot \vec{v}'_j - \vec{k} \cdot \vec{v}_j)} e^{i\vec{x}_j \cdot (\vec{k}' - \vec{k})} \sum_{s,u} \frac{2\alpha\beta^2\bar{c}}{\omega} e^{i(\vec{k} \cdot \vec{x}_s - \vec{k}' \cdot \vec{x}_u)} \text{Im}(R_{su}^{-1}(\omega)) \end{aligned} \quad (\text{D23a})$$

$$\begin{aligned} I_2(\omega) &= \frac{1}{(2\pi)^6} \int_V d^3v_j d^3v'_j \int d^3k d^3k' \frac{1}{(\nu + D_\rho k^2 - i\omega)(\nu + D_\rho k'^2 + i\omega)} \\ &\quad \cdot e^{i(\vec{k}' \cdot \vec{v}'_j - \vec{k} \cdot \vec{v}_j)} e^{i\vec{x}_j \cdot (\vec{k}' - \vec{k})} \sum_s \beta \bar{r}_s e^{i\vec{x}_s \cdot (\vec{k} - \vec{k}')} \end{aligned} \quad (\text{D23b})$$

$$\begin{aligned} I_3(\omega) &= \frac{1}{(2\pi)^6} \int_V d^3v_j d^3v'_j \int d^3k d^3k' \frac{1}{(\nu + D_\rho k^2 - i\omega)(\nu + D_\rho k'^2 + i\omega)} \\ &\quad \cdot e^{i(\vec{k}' \cdot \vec{v}'_j - \vec{k} \cdot \vec{v}_j)} e^{i\vec{x}_j \cdot (\vec{k}' - \vec{k})} \frac{2D_\rho \vec{k} \cdot \vec{k}'}{\nu + D_\rho |\vec{k} - \vec{k}'|^2} \sum_s \beta \bar{r}_s e^{i\vec{x}_s \cdot (\vec{k} - \vec{k}')}. \end{aligned} \quad (\text{D23c})$$

$$\begin{aligned} I_4(\omega) &= \frac{1}{(2\pi)^6} \int_V d^3v_j d^3v'_j \int d^3k d^3k' \frac{1}{(\nu + D_\rho k^2 - i\omega)(\nu + D_\rho k'^2 + i\omega)} \\ &\quad \cdot e^{i(\vec{k}' \cdot \vec{v}'_j - \vec{k} \cdot \vec{v}_j)} e^{i\vec{x}_j \cdot (\vec{k}' - \vec{k})} \frac{\nu}{\nu + D_\rho |\vec{k} - \vec{k}'|^2} \sum_s \beta \bar{r}_s e^{i\vec{x}_s \cdot (\vec{k} - \vec{k}')}. \end{aligned} \quad (\text{D23d})$$

Beginning with $I_1(\omega)$, moving the summation outside the integral and collecting terms exponential in \vec{k} and \vec{k}' yields

$$I_1(\omega) = \frac{2\alpha\beta^2\bar{c}}{(2\pi)^6 D_\rho^2 \omega} \sum_{s,u} \text{Im}(R_{su}^{-1}(\omega)) \int_V d^3 v_j d^3 v'_j \int d^3 k d^3 k' \cdot \frac{1}{\left(\frac{\nu-i\omega}{D_\rho} + k^2\right) \left(\frac{\nu+i\omega}{D_\rho} + k'^2\right)} e^{i\vec{k}\cdot(\vec{x}_s-\vec{x}_j-\vec{v}_j)} e^{-i\vec{k}'\cdot(\vec{x}_u-\vec{x}_j-\vec{v}'_j)}. \quad (\text{D24})$$

Inverting Eq. D14 allows for the k and k' integrals to be easily solved, simplifying $I_1(\omega)$ to

$$\begin{aligned} I_1(\omega) &= \frac{\alpha\beta^2\bar{c}}{2(2\pi D_\rho)^2 \omega} \sum_{s,u} \text{Im}(R_{su}^{-1}(\omega)) \int_V d^3 v_j d^3 v'_j \\ &\cdot \left(\frac{1}{|\vec{x}_p - \vec{x}_j - \vec{v}_j|} e^{-|\vec{x}_s - \vec{x}_j - \vec{v}_j| \sqrt{\frac{\nu-i\omega}{D_\rho}}} \right) \left(\frac{1}{|\vec{x}_u - \vec{x}_j - \vec{v}'_j|} e^{-|\vec{x}_u - \vec{x}_j - \vec{v}'_j| \sqrt{\frac{\nu+i\omega}{D_\rho}}} \right) \\ &= \frac{\alpha\beta^2\bar{c}a^4}{2D_\rho^2 \omega} \sum_{s,u} \text{Im}(R_{su}^{-1}(\omega)) \Lambda(|\vec{x}_s - \vec{x}_j|, a, \lambda(\omega)) \\ &\cdot \Lambda(|\vec{x}_u - \vec{x}_j|, a, \lambda(-\omega)), \end{aligned} \quad (\text{D25})$$

where a is the radius of the volume V ,

$$\lambda(\omega) \equiv \sqrt{\frac{D_\rho}{\nu-i\omega}} = \sqrt[4]{\frac{D_\rho^2}{4(\nu^2+\omega^2)}} \left(\sqrt{1 + \frac{\nu}{\sqrt{\nu^2+\omega^2}}} + i \text{sgn}(\omega) \sqrt{1 - \frac{\nu}{\sqrt{\nu^2+\omega^2}}} \right), \quad (\text{D26})$$

and

$$\Lambda(x, y, z) \equiv \begin{cases} \frac{2z^3}{xy^2} \left(\frac{x}{z} - \left(1 + \frac{y}{z}\right) e^{-\frac{y}{z}} \sinh\left(\frac{x}{z}\right) \right) & x < y \\ \frac{2z^3}{xy^2} e^{-\frac{x}{z}} \left(\frac{y}{z} \cosh\left(\frac{y}{z}\right) - \sinh\left(\frac{y}{z}\right) \right) & x > y \end{cases} \quad (\text{D27})$$

comes from the relation

$$\int_V d^3 z \frac{1}{|\vec{\kappa} - \vec{z}|} e^{-\frac{|\vec{\kappa} - \vec{z}|}{l}} = 2\pi a^2 \Lambda(\kappa, a, l), \quad (\text{D28})$$

which can be shown by writing \vec{z} in spherical coordinates and evaluating.

Moving to $I_2(\omega)$, following the exact same procedure as was done for $I_1(\omega)$ yields

$$\begin{aligned} I_2(\omega) &= \frac{\beta}{(2\pi)^6 D_\rho^2} \sum_s \bar{r}_s \int_V d^3 v_j d^3 v'_j \int d^3 k d^3 k' \\ &\cdot \frac{1}{\left(\frac{\nu-i\omega}{D_\rho} + k^2\right) \left(\frac{\nu+i\omega}{D_\rho} + k'^2\right)} e^{i\vec{k}\cdot(\vec{x}_s-\vec{x}_j-\vec{v}_j)} e^{-i\vec{k}'\cdot(\vec{x}_s-\vec{x}_j-\vec{v}'_j)} \\ &= \frac{\beta}{(4\pi D_\rho)^2} \sum_s \bar{r}_s \int_V d^3 v_j d^3 v'_j \\ &\cdot \left(\frac{1}{|\vec{x}_s - \vec{x}_j - \vec{v}_j|} e^{-|\vec{x}_s - \vec{x}_j - \vec{v}_j| \sqrt{\frac{\nu-i\omega}{D_\rho}}} \right) \left(\frac{1}{|\vec{x}_s - \vec{x}_j - \vec{v}'_j|} e^{-|\vec{x}_s - \vec{x}_j - \vec{v}'_j| \sqrt{\frac{\nu+i\omega}{D_\rho}}} \right) \\ &= \frac{\beta a^4}{4D_\rho^2} \sum_s \bar{r}_s |\Lambda(|\vec{x}_s - \vec{x}_j|, a, \lambda(\omega))|^2. \end{aligned} \quad (\text{D29})$$

Unfortunately, $I_3(\omega)$ cannot be solved by the same procedure as $I_1(\omega)$ and $I_2(\omega)$, but it can be solved. First, utilizing Eq. D14 again and letting $l = \sqrt{\frac{D_\rho}{\nu}}$ and $\vec{\kappa} = \vec{k} - \vec{k}'$ allows the factor of $\frac{2D_\rho}{\nu + D_\rho |\vec{k} - \vec{k}'|^2}$ to be transformed into

another integral, yielding

$$I_3(\omega) = \frac{1}{(2\pi)^7 D_\rho^2} \int_V d^3 v_j d^3 v'_j \int d^3 k d^3 k' d^3 z \frac{1}{\left(\frac{\nu-i\omega}{D_\rho} + k^2\right) \left(\frac{\nu+i\omega}{D_\rho} + k'^2\right)} \\ \cdot e^{i(\vec{k}' \cdot \vec{v}'_j - \vec{k} \cdot \vec{v}_j)} e^{i\vec{x}_j \cdot (\vec{k}' - \vec{k})} \frac{\vec{k} \cdot \vec{k}'}{z} e^{-z\sqrt{\frac{\nu}{D_\rho}}} e^{i\vec{z} \cdot (\vec{k} - \vec{k}')} \sum_s \beta \bar{r}_s e^{i\vec{x}_s \cdot (\vec{k} - \vec{k}')}.$$
 (D30)

Since v_j and v'_j only appear in a single exponential within the integrand, the factor of $\vec{k} \cdot \vec{k}'$ can be replaced by $\vec{\nabla}_{v_j} \cdot \vec{\nabla}_{v'_j}$ acting on the exponential. The gradient operators can then be moved outside the k , k' , and z integrals while the summation is moved outside of all the integrals to produce

$$I_3(\omega) = \frac{\beta}{(2\pi)^7 D_\rho^2} \sum_s \bar{r}_s \int_V d^3 v_j d^3 v'_j \vec{\nabla}_{v_j} \cdot \vec{\nabla}_{v'_j} \int d^3 k d^3 k' d^3 z \frac{1}{\left(\frac{\nu-i\omega}{D_\rho} + k^2\right) \left(\frac{\nu+i\omega}{D_\rho} + k'^2\right)} \\ \cdot \frac{1}{z} e^{-z\sqrt{\frac{\nu}{D_\rho}}} e^{i(\vec{k}' \cdot \vec{v}'_j - \vec{k} \cdot \vec{v}_j)} e^{i\vec{x}_j \cdot (\vec{k}' - \vec{k})} e^{i\vec{z} \cdot (\vec{k} - \vec{k}')} e^{i\vec{x}_s \cdot (\vec{k} - \vec{k}')}.$$
 (D31)

Utilizing the inverse of Eq. D14 to solve the k and k' integrals then yields

$$I_3(\omega) = \frac{\beta}{4(2\pi)^3 D_\rho^2} \sum_s \bar{r}_s \int_V d^3 v_j d^3 v'_j \vec{\nabla}_{v_j} \cdot \vec{\nabla}_{v'_j} \int d^3 z \frac{1}{z} e^{-z\sqrt{\frac{\nu}{D_\rho}}} \\ \cdot \left(\frac{1}{|\vec{z} + \vec{x}_s - \vec{x}_j - \vec{v}_j|} e^{-|\vec{z} + \vec{x}_s - \vec{x}_j - \vec{v}_j| \sqrt{\frac{\nu-i\omega}{D_\rho}}} \right) \left(\frac{1}{|\vec{z} + \vec{x}_s - \vec{x}_j - \vec{v}'_j|} e^{-|\vec{z} + \vec{x}_s - \vec{x}_j - \vec{v}'_j| \sqrt{\frac{\nu+i\omega}{D_\rho}}} \right).$$
 (D32)

From here the z integral can be moved outside the v_j and v'_j integrals, which can in turn be separated into the product of two independent integrals to produce

$$I_3(\omega) = \frac{\beta}{4(2\pi)^3 D_\rho^2} \sum_s \bar{r}_s \int d^3 z \frac{1}{z} e^{-z\sqrt{\frac{\nu}{D_\rho}}} \left(\int_V d^3 v_j \vec{\nabla}_{v_j} \frac{1}{|\vec{z} + \vec{x}_s - \vec{x}_j - \vec{v}_j|} e^{-|\vec{z} + \vec{x}_s - \vec{x}_j - \vec{v}_j| \sqrt{\frac{\nu-i\omega}{D_\rho}}} \right) \\ \cdot \left(\int_V d^3 v'_j \vec{\nabla}_{v'_j} \frac{1}{|\vec{z} + \vec{x}_s - \vec{x}_j - \vec{v}'_j|} e^{-|\vec{z} + \vec{x}_s - \vec{x}_j - \vec{v}'_j| \sqrt{\frac{\nu+i\omega}{D_\rho}}} \right).$$
 (D33)

Due to the fact that the v_j and v'_j integrands in Eq. D33 depend only on $|\vec{z} + \vec{x}_s - \vec{x}_j - \vec{v}_j|$ and $|\vec{z} + \vec{x}_s - \vec{x}_j - \vec{v}'_j|$ respectively, taking the gradient with respect to v_j and v'_j is identical to taking the gradient with respect to z and multiplying by a factor of -1 in both cases. The extra factors of -1 can be ignored, however, as they will multiply to unity. This allows the gradients to be moved outside of the v_j and v'_j integrals, which in turn allows them to be solved via Eq. D28 to produce

$$I_3(\omega) = \frac{\beta a^4}{8\pi D_\rho^2} \sum_s \bar{r}_s \int d^3 z \frac{1}{z} e^{-z\sqrt{\frac{\nu}{D_\rho}}} \left| \vec{\nabla}_z \Lambda(|\vec{z} + \vec{x}_s - \vec{x}_j|, a, \lambda(\omega)) \right|^2.$$
 (D34)

Let $\vec{y} = \vec{z} + \vec{x}_s - \vec{x}_j$. Since the z integral is over all of z -space, this transformation does not change the limits of integration. Additionally, $d^3 y = d^3 z$ and $\vec{\nabla}_y = \vec{\nabla}_z$ since y and z are related by a simple translation. This transformation allows Eq. D34 to be written as

$$I_3(\omega) = \frac{\beta a^4}{8\pi D_\rho^2} \sum_s \bar{r}_s \int d^3 y \frac{1}{|\vec{y} + \vec{x}_j - \vec{x}_s|} e^{-|\vec{y} + \vec{x}_j - \vec{x}_s| \sqrt{\frac{\nu}{D_\rho}}} \left| \vec{\nabla}_y \Lambda(y, a, \lambda(\omega)) \right|^2.$$
 (D35)

Let V_y be the spherical volume in y -space centered at the origin with radius a and V'_y be all of y -space excluding V_y . These along with Eq. D27 allow the integral in Eq. D35 to be broken into two separate pieces along the piecewise

boundary of $\Lambda(y, a, \lambda(\omega))$ to produce

$$\begin{aligned}
I_3(\omega) = & \frac{\beta a^4}{8\pi D_\rho^2} \sum_s \bar{r}_s \int_{V_y} d^3y \frac{1}{|\vec{y} + \vec{x}_j - \vec{x}_s|} e^{-|\vec{y} + \vec{x}_j - \vec{x}_s| \sqrt{\frac{\nu}{D_\rho}}} \\
& \cdot \left| \vec{\nabla}_y \frac{2}{y a^2} \left(\frac{D_\rho}{\nu - i\omega} \right)^{\frac{3}{2}} \left(y \sqrt{\frac{\nu - i\omega}{D_\rho}} - \left(1 + a \sqrt{\frac{\nu - i\omega}{D_\rho}} \right) e^{-a \sqrt{\frac{\nu - i\omega}{D_\rho}}} \sinh \left(y \sqrt{\frac{\nu - i\omega}{D_\rho}} \right) \right) \right|^2 \\
& + \int_{V'_y} d^3y \frac{1}{|\vec{y} + \vec{x}_j - \vec{x}_s|} e^{-|\vec{y} + \vec{x}_j - \vec{x}_s| \sqrt{\frac{\nu}{D_\rho}}} \\
& \cdot \left| \vec{\nabla}_y \frac{2}{y a^2} \left(\frac{D_\rho}{\nu - i\omega} \right)^{\frac{3}{2}} e^{-y \sqrt{\frac{\nu - i\omega}{D_\rho}}} \left(a \sqrt{\frac{\nu - i\omega}{D_\rho}} \cosh \left(a \sqrt{\frac{\nu - i\omega}{D_\rho}} \right) - \sinh \left(a \sqrt{\frac{\nu - i\omega}{D_\rho}} \right) \right) \right|^2. \tag{D36}
\end{aligned}$$

Performing the gradient operators then yields

$$\begin{aligned}
I_3(\omega) = & \frac{\beta a^4}{8\pi D_\rho^2} \sum_s \bar{r}_s \int_{V_y} d^3y \frac{1}{|\vec{y} + \vec{x}_j - \vec{x}_s|} e^{-\frac{|\vec{y} + \vec{x}_j - \vec{x}_s|}{\lambda(0)}} \\
& \cdot \left| \frac{\vec{y}}{y} \frac{2(\lambda(\omega))^3}{y^2 a^2} \left(1 + \frac{a}{\lambda(\omega)} \right) e^{-\frac{a}{\lambda(\omega)}} \left(\sinh \left(\frac{y}{\lambda(\omega)} \right) \right. \right. \\
& \quad \left. \left. - \frac{y}{\lambda(\omega)} \cosh \left(\frac{y}{\lambda(\omega)} \right) \right) \right|^2 + \int_{V'_y} d^3y \frac{1}{|\vec{y} + \vec{x}_j - \vec{x}_s|} e^{-\frac{|\vec{y} + \vec{x}_j - \vec{x}_s|}{\lambda(0)}} \\
& \cdot \left| \frac{\vec{y}}{y} \frac{2(\lambda(\omega))^3}{y^2 a^2} \left(1 + \frac{y}{\lambda(\omega)} \right) e^{-\frac{y}{\lambda(\omega)}} \left(\sinh \left(\frac{a}{\lambda(\omega)} \right) \right. \right. \\
& \quad \left. \left. - \frac{a}{\lambda(\omega)} \cosh \left(\frac{a}{\lambda(\omega)} \right) \right) \right|^2. \tag{D37}
\end{aligned}$$

Once the magnitude squared of each vector is taken, the only term in either integral that depends on the angle of \vec{y} will be $|\vec{y} + \vec{x}_j - \vec{x}_s|$. Thus, the angular portion of each integral can be performed to yield

$$\begin{aligned}
I_3(\omega) = & \frac{\beta |\lambda(\omega)|^6}{D_\rho^2} \sum_s \bar{r}_s \int_0^a dy \frac{\lambda(0)}{y^3 |\vec{x}_s - \vec{x}_j|} \left(e^{-\frac{|y - |\vec{x}_s - \vec{x}_j||}{\lambda(0)}} - e^{-\frac{y + |\vec{x}_s - \vec{x}_j|}{\lambda(0)}} \right) \\
& \cdot \left| \left(1 + \frac{a}{\lambda(\omega)} \right) e^{-\frac{a}{\lambda(\omega)}} \left(\sinh \left(\frac{y}{\lambda(\omega)} \right) - \frac{y}{\lambda(\omega)} \cosh \left(\frac{y}{\lambda(\omega)} \right) \right) \right|^2 \\
& + \int_a^\infty dy \frac{\lambda(0)}{y^3 |\vec{x}_s - \vec{x}_j|} \left(e^{-\frac{|y - |\vec{x}_s - \vec{x}_j||}{\lambda(0)}} - e^{-\frac{y + |\vec{x}_s - \vec{x}_j|}{\lambda(0)}} \right) \\
& \cdot \left| \left(1 + \frac{y}{\lambda(\omega)} \right) e^{-\frac{y}{\lambda(\omega)}} \left(\sinh \left(\frac{a}{\lambda(\omega)} \right) - \frac{a}{\lambda(\omega)} \cosh \left(\frac{a}{\lambda(\omega)} \right) \right) \right|^2. \tag{D38}
\end{aligned}$$

The integrals in Eq. D38 are well defined and very involved. Nonetheless, they can be performed piece-by-piece with the aid of integral tables or symbolic computational solvers. The result is

$$\begin{aligned}
I_3(\omega) = & \frac{\beta a^4}{D_\rho^2} \sum_s \bar{r}_s \left(\frac{\left| \left(1 + \frac{a}{\lambda(\omega)} \right) e^{-\frac{a}{\lambda(\omega)}} \right|^2}{18} \Upsilon(|\vec{x}_s - \vec{x}_j|, a, \lambda(0), \lambda(\omega)) \right. \\
& \left. + \left| \left(\frac{\lambda(\omega)}{a} \right)^3 \left(\sinh \left(\frac{a}{\lambda(\omega)} \right) - \frac{a}{\lambda(\omega)} \cosh \left(\frac{a}{\lambda(\omega)} \right) \right) \right|^2 \Xi(|\vec{x}_s - \vec{x}_j|, a, \lambda(0), \lambda(\omega)) \right), \tag{D39}
\end{aligned}$$

where

$$\Upsilon(x, y, z, w) \equiv \begin{cases} \frac{9z|w|^6 \sinh(\frac{x}{z})}{xy^6} e^{-\frac{y}{z}} \left(2y \operatorname{Re} \left(\frac{1}{w} \right) \sinh \left(2y \operatorname{Re} \left(\frac{1}{w} \right) \right) + 2y \operatorname{Im} \left(\frac{1}{w} \right) \sin \left(2y \operatorname{Im} \left(\frac{1}{w} \right) \right) \right. \\ \quad \left. - \left(1 - \frac{y}{z} \right) \left(\cosh \left(2y \operatorname{Re} \left(\frac{1}{w} \right) \right) - \cos \left(2y \operatorname{Im} \left(\frac{1}{w} \right) \right) \right) \right) \\ \quad - \frac{9|w|^6}{x^2 y^4} \left(\cosh \left(2x \operatorname{Re} \left(\frac{1}{w} \right) \right) - \cos \left(2x \operatorname{Im} \left(\frac{1}{w} \right) \right) \right) \\ \quad - \frac{9|w|^6}{2xy^4 z} e^{-\frac{x}{z}} \left(\operatorname{Shi} \left(x \left(\frac{1}{z} + 2 \operatorname{Re} \left(\frac{1}{w} \right) \right) \right) + \operatorname{Shi} \left(x \left(\frac{1}{z} - 2 \operatorname{Re} \left(\frac{1}{w} \right) \right) \right) \right. \\ \quad \left. - \operatorname{Shi} \left(x \left(\frac{1}{z} + 2i \operatorname{Im} \left(\frac{1}{w} \right) \right) \right) - \operatorname{Shi} \left(x \left(\frac{1}{z} - 2i \operatorname{Im} \left(\frac{1}{w} \right) \right) \right) \right) \\ \quad - \frac{9|w|^6 \sinh(\frac{x}{z})}{2xy^4 z} \left(\operatorname{Ei} \left(x \left(\frac{1}{z} + 2 \operatorname{Re} \left(\frac{1}{w} \right) \right) \right) + \operatorname{Ei} \left(x \left(\frac{1}{z} - 2 \operatorname{Re} \left(\frac{1}{w} \right) \right) \right) \right. \\ \quad \left. - \operatorname{Ei} \left(x \left(\frac{1}{z} + 2i \operatorname{Im} \left(\frac{1}{w} \right) \right) \right) - \operatorname{Ei} \left(x \left(\frac{1}{z} - 2i \operatorname{Im} \left(\frac{1}{w} \right) \right) \right) \right) \\ \quad - \operatorname{Ei} \left(y \left(\frac{1}{z} + 2 \operatorname{Re} \left(\frac{1}{w} \right) \right) \right) - \operatorname{Ei} \left(y \left(\frac{1}{z} - 2 \operatorname{Re} \left(\frac{1}{w} \right) \right) \right) \\ \quad \left. + \operatorname{Ei} \left(y \left(\frac{1}{z} + 2i \operatorname{Im} \left(\frac{1}{w} \right) \right) \right) + \operatorname{Ei} \left(y \left(\frac{1}{z} - 2i \operatorname{Im} \left(\frac{1}{w} \right) \right) \right) \right) \quad x < y \\ \frac{9z|w|^6 \sinh(\frac{y}{z})}{xy^6} e^{-\frac{x}{z}} \left(2y \operatorname{Re} \left(\frac{1}{w} \right) \sinh \left(2y \operatorname{Re} \left(\frac{1}{w} \right) \right) + 2y \operatorname{Im} \left(\frac{1}{w} \right) \sin \left(2y \operatorname{Im} \left(\frac{1}{w} \right) \right) \right) \\ \quad - \frac{9z|w|^6 \left(\sinh(\frac{y}{z}) + \frac{y}{z} \cosh(\frac{y}{z}) \right)}{xy^6} e^{-\frac{x}{z}} \left(\cosh \left(2y \operatorname{Re} \left(\frac{1}{w} \right) \right) - \cos \left(2y \operatorname{Im} \left(\frac{1}{w} \right) \right) \right) \\ \quad - \frac{9|w|^6}{2xy^4 z} e^{-\frac{x}{z}} \left(\operatorname{Shi} \left(y \left(\frac{1}{z} + 2 \operatorname{Re} \left(\frac{1}{w} \right) \right) \right) + \operatorname{Shi} \left(y \left(\frac{1}{z} - 2 \operatorname{Re} \left(\frac{1}{w} \right) \right) \right) \right. \\ \quad \left. - \operatorname{Shi} \left(y \left(\frac{1}{z} + 2i \operatorname{Im} \left(\frac{1}{w} \right) \right) \right) - \operatorname{Shi} \left(y \left(\frac{1}{z} - 2i \operatorname{Im} \left(\frac{1}{w} \right) \right) \right) \right) \quad x > y, \end{cases} \quad (\text{D40})$$

$$\Xi(x, y, z, w) \equiv \begin{cases} \frac{z \sinh(\frac{x}{z})}{x} \left(\left(1 + y \left(2 \operatorname{Re} \left(\frac{1}{w} \right) - \frac{1}{z} \right) \right) e^{-y \left(2 \operatorname{Re} \left(\frac{1}{w} \right) + \frac{1}{z} \right)} - \frac{y^2}{z^2} \operatorname{Ei} \left(y \left(2 \operatorname{Re} \left(\frac{1}{w} \right) + \frac{1}{z} \right) \right) \right) \quad x < y \\ \frac{z}{x} e^{-\frac{x}{z}} \left(e^{-2y \operatorname{Re} \left(\frac{1}{w} \right)} \left(\left(1 + 2y \operatorname{Re} \left(\frac{1}{w} \right) \right) \sinh \left(\frac{y}{z} \right) + \frac{y}{z} \cosh \left(\frac{y}{z} \right) \right) \right. \\ \quad \left. - \frac{y^2}{2z^2} \left(e^{\frac{2x}{z}} \operatorname{Ei} \left(x \left(2 \operatorname{Re} \left(\frac{1}{w} \right) + \frac{1}{z} \right) \right) - \operatorname{Ei} \left(x \left(2 \operatorname{Re} \left(\frac{1}{w} \right) - \frac{1}{z} \right) \right) \right) \right. \\ \quad \left. - \operatorname{Ei} \left(y \left(2 \operatorname{Re} \left(\frac{1}{w} \right) + \frac{1}{z} \right) \right) + \operatorname{Ei} \left(y \left(2 \operatorname{Re} \left(\frac{1}{w} \right) - \frac{1}{z} \right) \right) \right) - \frac{y^2}{xz} e^{-x \left(2 \operatorname{Re} \left(\frac{1}{w} \right) - \frac{1}{z} \right)} \quad x > y, \end{cases} \quad (\text{D41})$$

$$\operatorname{Shi}(x) \equiv \int_0^x dt \frac{\sinh(t)}{t}, \quad (\text{D42})$$

and

$$\operatorname{Ei}(x) \equiv \int_x^\infty dt \frac{e^{-t}}{t}. \quad (\text{D43})$$

Lastly, $I_4(\omega)$ must be solved. Similarly utilizing Eq. D14 allows Eq. D23d to be transformed into

$$I_4(\omega) = \frac{\nu}{2(2\pi)^7 D_\rho^3} \int_V d^3 v_j d^3 v'_j \int d^3 k d^3 k' d^3 z \frac{1}{\left(\frac{\nu - i\omega}{D_\rho} + k^2 \right) \left(\frac{\nu + i\omega}{D_\rho} + k'^2 \right)} \\ \cdot e^{i(\vec{k}' \cdot \vec{v}'_j - \vec{k} \cdot \vec{v}_j)} e^{i\vec{x}_j \cdot (\vec{k} - \vec{k}')} \frac{1}{z} e^{-z \sqrt{\frac{\nu}{D_\rho}}} e^{i\vec{z} \cdot (\vec{k} - \vec{k}')} \sum_s \beta \bar{r}_s e^{i\vec{x}_s \cdot (\vec{k} - \vec{k}')} \quad (\text{D44})$$

Utilizing the inverse of Eq. D14 to solve the k and k' integrals then yields

$$I_4(\omega) = \frac{\beta \nu}{8(2\pi)^3 D_\rho^3} \sum_s \bar{r}_s \int_V d^3 v_j d^3 v'_j \int d^3 z \frac{1}{z} e^{-z \sqrt{\frac{\nu}{D_\rho}}} \\ \cdot \left(\frac{1}{|\vec{z} + \vec{x}_s - \vec{x}_j - \vec{v}_j|} e^{-|\vec{z} + \vec{x}_s - \vec{x}_j - \vec{v}_j| \sqrt{\frac{\nu - i\omega}{D_\rho}}} \right) \left(\frac{1}{|\vec{z} + \vec{x}_s - \vec{x}_j - \vec{v}'_j|} e^{-|\vec{z} + \vec{x}_s - \vec{x}_j - \vec{v}'_j| \sqrt{\frac{\nu + i\omega}{D_\rho}}} \right). \quad (\text{D45})$$

From here the z integral can be moved outside the v_j and v'_j integrals, which can in turn be separated into the product of two independent integrals to produce

$$I_4(\omega) = \frac{\beta \nu}{8(2\pi)^3 D_\rho^3} \sum_s \bar{r}_s \int d^3 z \frac{1}{z} e^{-z \sqrt{\frac{\nu}{D_\rho}}} \left(\int_V d^3 v_j \frac{1}{|\vec{z} + \vec{x}_s - \vec{x}_j - \vec{v}_j|} e^{-|\vec{z} + \vec{x}_s - \vec{x}_j - \vec{v}_j| \sqrt{\frac{\nu - i\omega}{D_\rho}}} \right) \\ \cdot \left(\int_V d^3 v'_j \frac{1}{|\vec{z} + \vec{x}_s - \vec{x}_j - \vec{v}'_j|} e^{-|\vec{z} + \vec{x}_s - \vec{x}_j - \vec{v}'_j| \sqrt{\frac{\nu + i\omega}{D_\rho}}} \right). \quad (\text{D46})$$

The v_j and v'_j integrals can then be solved via Eq. D28 to produce

$$I_4(\omega) = \frac{\beta\nu a^4}{16\pi D_\rho^3} \sum_s \bar{r}_s \int d^3z \frac{1}{z} e^{-z\sqrt{\frac{\nu}{D_\rho}}} |\Lambda(|\vec{z} + \vec{x}_s - \vec{x}_j|, a, \lambda(\omega))|^2. \quad (D47)$$

Again, let $\vec{y} = \vec{z} + \vec{x}_s - \vec{x}_j$ as well as V_y be the spherical volume in y -space centered at the origin with radius a and V'_y be all of y -space excluding V_y . These transformations allow the Λ function to be split along its piecewise boundary again and Eq. D47 to be written as

$$\begin{aligned} I_4(\omega) = & \frac{\beta\nu a^4}{16\pi D_\rho^3} \sum_s \bar{r}_s \int_{V_y} d^3y \frac{1}{|\vec{y} + \vec{x}_j - \vec{x}_s|} e^{-|\vec{y} + \vec{x}_j - \vec{x}_s|\sqrt{\frac{\nu}{D_\rho}}} \\ & \cdot \left| \frac{2(\lambda(\omega))^3}{ya^2} \left(\frac{y}{\lambda(\omega)} - \left(1 + \frac{a}{\lambda(\omega)}\right) e^{-\frac{a}{\lambda(\omega)}} \sinh\left(\frac{y}{\lambda(\omega)}\right) \right) \right|^2 \\ & + \int_{V'_y} d^3y \frac{1}{|\vec{y} + \vec{x}_j - \vec{x}_s|} e^{-|\vec{y} + \vec{x}_j - \vec{x}_s|\sqrt{\frac{\nu}{D_\rho}}} \\ & \cdot \left| \frac{2(\lambda(\omega))^3}{ya^2} e^{-\frac{y}{\lambda(\omega)}} \left(\frac{a}{\lambda(\omega)} \cosh\left(\frac{a}{\lambda(\omega)}\right) - \sinh\left(\frac{a}{\lambda(\omega)}\right) \right) \right|^2. \end{aligned} \quad (D48)$$

Once again, the only term in either integral that depends on the angle of \vec{y} will be $|\vec{y} + \vec{x}_j - \vec{x}_s|$. Thus, the angular portion of each integral can be performed to yield

$$\begin{aligned} I_4(\omega) = & \frac{\beta\nu |\lambda(\omega)|^6}{2D_\rho^3} \sum_s \bar{r}_s \int_0^a dy \frac{\lambda(0)}{y|\vec{x}_s - \vec{x}_j|} \left(e^{-\frac{|y - |\vec{x}_s - \vec{x}_j||}{\lambda(0)}} - e^{-\frac{y + |\vec{x}_s - \vec{x}_j|}{\lambda(0)}} \right) \\ & \cdot \left| \frac{y}{\lambda(\omega)} - \left(1 + \frac{a}{\lambda(\omega)}\right) e^{-\frac{a}{\lambda(\omega)}} \sinh\left(\frac{y}{\lambda(\omega)}\right) \right|^2 \\ & + \int_a^\infty dy \frac{\lambda(0)}{y|\vec{x}_s - \vec{x}_j|} \left(e^{-\frac{|y - |\vec{x}_s - \vec{x}_j||}{\lambda(0)}} - e^{-\frac{y + |\vec{x}_s - \vec{x}_j|}{\lambda(0)}} \right) \\ & \cdot \left| e^{-\frac{y}{\lambda(\omega)}} \left(\frac{a}{\lambda(\omega)} \cosh\left(\frac{a}{\lambda(\omega)}\right) - \sinh\left(\frac{a}{\lambda(\omega)}\right) \right) \right|^2. \end{aligned} \quad (D49)$$

Relying again on integral tables or computational solvers, these integrals can also be performed and yield

$$I_4(\omega) = \frac{\beta\nu |\lambda(\omega)|^6}{2D_\rho^3} \sum_s \bar{r}_s (\Psi(|\vec{x}_s - \vec{x}_j|, a, \lambda(0), \lambda(\omega)) + \Omega(|\vec{x}_s - \vec{x}_j|, a, \lambda(0), \lambda(\omega))) \quad (D50)$$

where

$$\Psi(x, y, z, w) = \begin{cases} \frac{2z^3}{x|w|^2} \left(\frac{x}{z} - \left(1 + \frac{y}{z}\right) e^{-\frac{y}{z}} \sinh\left(\frac{x}{z}\right) \right) \\ + \text{Re} \left(\frac{4z^2 w}{xw^*} \frac{1 + \frac{y}{w}}{w^2 - z^2} \left(ze^{-\frac{y}{z}} \sinh\left(\frac{x}{z}\right) + we^{-\frac{y}{w}} \sinh\left(\frac{x}{w}\right) \right) \right) \\ + \frac{z}{2x} \left| \left(1 + \frac{y}{w}\right) e^{-\frac{y}{w}} \right|^2 \left(e^{-\frac{x}{z}} \left(\text{Shi}\left(x\left(\frac{1}{z} + 2\text{Re}\left(\frac{1}{w}\right)\right)\right) \right. \right. \right. \\ + \text{Shi}\left(x\left(\frac{1}{z} - 2\text{Re}\left(\frac{1}{w}\right)\right)\right) - \text{Shi}\left(x\left(\frac{1}{z} + 2i\text{Im}\left(\frac{1}{w}\right)\right)\right) \\ \left. \left. - \text{Shi}\left(x\left(\frac{1}{z} - 2i\text{Im}\left(\frac{1}{w}\right)\right)\right) \right) + \sinh\left(\frac{x}{z}\right) \left(\text{Ei}\left(x\left(\frac{1}{z} + 2\text{Re}\left(\frac{1}{w}\right)\right)\right) \right. \right. \right. \\ + \text{Ei}\left(x\left(\frac{1}{z} - 2\text{Re}\left(\frac{1}{w}\right)\right)\right) - \text{Ei}\left(x\left(\frac{1}{z} + 2i\text{Im}\left(\frac{1}{w}\right)\right)\right) \\ \left. \left. - \text{Ei}\left(x\left(\frac{1}{z} - 2i\text{Im}\left(\frac{1}{w}\right)\right)\right) - \text{Ei}\left(y\left(\frac{1}{z} + 2\text{Re}\left(\frac{1}{w}\right)\right)\right) \right. \right. \right. \\ - \text{Ei}\left(y\left(\frac{1}{z} - 2\text{Re}\left(\frac{1}{w}\right)\right)\right) + \text{Ei}\left(y\left(\frac{1}{z} + 2i\text{Im}\left(\frac{1}{w}\right)\right)\right) \\ \left. \left. + \text{Ei}\left(y\left(\frac{1}{z} - 2i\text{Im}\left(\frac{1}{w}\right)\right)\right) \right) \right) \quad x < y \\ \frac{2z^3}{x|w|^2} e^{-\frac{x}{z}} \left(\frac{y}{z} \cosh\left(\frac{y}{z}\right) - \sinh\left(\frac{y}{z}\right) \right) \\ + \text{Re} \left(\frac{4z^2 w}{xw^*} \frac{1 + \frac{y}{w}}{w^2 - z^2} e^{-\frac{x}{z}} \left((w + z) \sinh\left(y\left(\frac{1}{z} - \frac{1}{w}\right)\right) \right. \right. \right. \\ - (w - z) \sinh\left(y\left(\frac{1}{z} + \frac{1}{w}\right)\right) \left. \left. \right) \right) \\ + \frac{z}{2x} \left| \left(1 + \frac{y}{w}\right) e^{-\frac{y}{w}} \right|^2 e^{-\frac{x}{z}} \left(\text{Shi}\left(a\left(\frac{1}{z} + 2\text{Re}\left(\frac{1}{w}\right)\right)\right) \right. \right. \right. \\ + \text{Shi}\left(a\left(\frac{1}{z} - 2\text{Re}\left(\frac{1}{w}\right)\right)\right) - \text{Shi}\left(a\left(\frac{1}{z} + 2i\text{Im}\left(\frac{1}{w}\right)\right)\right) \\ \left. \left. - \text{Shi}\left(a\left(\frac{1}{z} - 2i\text{Im}\left(\frac{1}{w}\right)\right)\right) \right) \right) \quad x > y, \end{cases} \quad (D51)$$

and

$$\Omega(x, y, z, w) = \begin{cases} \frac{2z}{x} \sinh\left(\frac{x}{z}\right) \left| \frac{y}{w} \cosh\left(\frac{y}{w}\right) - \sinh\left(\frac{y}{w}\right) \right|^2 \text{Ei}\left(y\left(\frac{1}{z} + 2\text{Re}\left(\frac{1}{w}\right)\right)\right) & x < y \\ \frac{2z}{x} \sinh\left(\frac{x}{z}\right) \left| \frac{y}{w} \cosh\left(\frac{y}{w}\right) - \sinh\left(\frac{y}{w}\right) \right|^2 \text{Ei}\left(x\left(\frac{1}{z} + 2\text{Re}\left(\frac{1}{w}\right)\right)\right) \\ + \frac{z}{x} e^{-\frac{x}{z}} \left| \frac{y}{w} \cosh\left(\frac{y}{w}\right) - \sinh\left(\frac{y}{w}\right) \right|^2 \left(\text{Ei}\left(y\left(2\text{Re}\left(\frac{1}{w}\right) - \frac{1}{z}\right)\right) \right. \\ \left. - \text{Ei}\left(y\left(2\text{Re}\left(\frac{1}{w}\right) + \frac{1}{z}\right)\right) - \text{Ei}\left(x\left(2\text{Re}\left(\frac{1}{w}\right) - \frac{1}{z}\right)\right) \right. \\ \left. + \text{Ei}\left(x\left(2\text{Re}\left(\frac{1}{w}\right) + \frac{1}{z}\right)\right)\right) & x > y. \end{cases} \quad (\text{D52})$$

With the power spectrum of $m_j(t)$ solved, the mean \bar{m}_j needs to now be calculated in order to obtain the noise-to-signal ratio. Combining Eqs. D3 and D19 yields

$$\bar{m}_j = \int_{V_j} d^3x \frac{1}{4\pi D_\rho} \sum_l \frac{\beta \bar{r}_l}{|\vec{x} - \vec{x}_l|} e^{-|\vec{x} - \vec{x}_l| \sqrt{\frac{\nu}{D_\rho}}}. \quad (\text{D53})$$

Again, let $\vec{v}_j = \vec{x} - \vec{x}_j$. Utilizing this substitution and Eq. D28 to solve Eq. D53 yields

$$\begin{aligned} \bar{m}_j &= \frac{\beta}{4\pi D_\rho} \sum_l \bar{r}_l \int_{V_j} d^3v_j \frac{1}{|\vec{v}_j - (\vec{x}_l - \vec{x}_j)|} e^{-|\vec{v}_j - (\vec{x}_l - \vec{x}_j)| \sqrt{\frac{\nu}{D_\rho}}} \\ &= \frac{\beta a^2}{2D_\rho} \sum_l \bar{r}_l \Lambda(|\vec{x}_l - \vec{x}_j|, a, \lambda(0)) \end{aligned} \quad (\text{D54})$$

Finally, combining Eqs. D22, D25, D29, D39, D50, and D54 yields the time averaged noise-to-signal ratio of $m_j(t)$. To determine the criteria for T in this equation, it is important to note that ω only appears in $\lambda(\omega)$, which directly compares ω to ν in Eq. D26. However, ν can be taken to 0 without complication, thus leaving ω to be directly compared to $\frac{D_\rho}{a^2}$ as $\lambda(\omega)$ is always found in proportion to a or $|\vec{x}_i - \vec{x}_j|$, but $|\vec{x}_i - \vec{x}_j|$ can be taken to ∞ without complication as well. Thus, $\omega \ll \nu$ must be true unless $\nu \ll \frac{D_\rho}{a^2}$, at which point $\omega \ll \frac{D_\rho}{a^2}$ must be true. This in turn implies $T \gg \tau_4 = \left(\nu + \frac{D_\rho}{a^2}\right)^{-1}$ can be taken as the appropriate criterion for T . Once this is met, the time averaged noise-to-signal ratio of $m_j(t)$ can be calculated to be

$$\begin{aligned} \frac{(\delta m_j)^2}{\bar{m}_j^2} &= \frac{S_m(0)}{\bar{m}_j^2 T} = \frac{1}{\bar{m}_j^2 T} \int \frac{d\omega'}{2\pi} \left\langle \delta \tilde{m}_j^*(\omega') \delta \tilde{m}_j(0) \right\rangle \\ &= \frac{I_1(0) + I_2(0) + I_3(0) + I_4(0)}{\left(\frac{\beta a^2}{2D_\rho} \sum_l \bar{r}_l \Lambda(|\vec{x}_l - \vec{x}_j|, a, \lambda(0))\right)^2 T} \\ &= \frac{1}{\beta T} \left(\sum_l \bar{r}_l \Lambda(|\vec{x}_l - \vec{x}_j|, a, \lambda(0)) \right)^{-2} \left(\sum_s \bar{r}_s |\Lambda(|\vec{x}_s - \vec{x}_j|, a, \lambda(0))|^2 \right. \\ &\quad + \sum_{s,u} 2\alpha\beta\bar{c} \lim_{\omega \rightarrow 0} \left(\frac{1}{\omega} \text{Im}(R_{su}^{-1}(\omega)) \right) \Lambda(|\vec{x}_s - \vec{x}_j|, a, \lambda(0)) \Lambda(|\vec{x}_u - \vec{x}_j|, a, \lambda(0)) \\ &\quad + \sum_s 4\bar{r}_s \left(\frac{\left| \left(1 + \frac{a}{\lambda(0)}\right) e^{-\frac{a}{\lambda(0)}} \right|^2}{18} \Upsilon(|\vec{x}_s - \vec{x}_j|, a, \lambda(0), \lambda(0)) \right. \\ &\quad + \left| \left(\frac{\lambda(0)}{a} \right)^3 \left(\sinh\left(\frac{a}{\lambda(0)}\right) - \frac{a}{\lambda(0)} \cosh\left(\frac{a}{\lambda(0)}\right) \right) \right|^2 \Xi(|\vec{x}_s - \vec{x}_j|, a, \lambda(0), \lambda(0)) \\ &\quad \left. \left. + \sum_s 2\bar{r}_s \left(\frac{\lambda(0)}{a} \right)^4 (\Psi(|\vec{x}_s - \vec{x}_j|, a, \lambda(0), \lambda(0)) + \Omega(|\vec{x}_s - \vec{x}_j|, a, \lambda(0), \lambda(0))) \right) \right) \end{aligned} \quad (\text{D55})$$

Eq. D55 can be greatly simplified in form under the limit $\nu \ll \frac{D_\rho}{a^2}$, which by Eq. D26 implies $\lambda(0) \gg a$. When this limit is taken, the Ψ and Ω functions vanish due to their original multiplication by ν in Eq. D23d while the Λ , Υ , and

Ξ functions simplify to

$$\lim_{z \rightarrow \infty} \Lambda(x, y, z) \equiv \Lambda_\infty \left(\frac{x}{y} \right) = \begin{cases} 1 - \frac{1}{3} \left(\frac{x}{y} \right)^2 & \frac{x}{y} < 1 \\ \frac{2y}{3x} & \frac{x}{y} > 1, \end{cases} \quad (\text{D56a})$$

$$\lim_{z \rightarrow \infty} \Upsilon(x, y, z, z) \equiv \Upsilon_\infty \left(\frac{x}{y} \right) = \begin{cases} 1 - \frac{1}{5} \left(\frac{x}{y} \right)^4 & \frac{x}{y} < 1 \\ \frac{4y}{5x} & \frac{x}{y} > 1, \end{cases} \quad (\text{D56b})$$

$$\lim_{z \rightarrow \infty} \Xi(x, y, z, z) \equiv \Xi_\infty \left(\frac{x}{y} \right) = \begin{cases} 1 & \frac{x}{y} < 1 \\ \frac{2y}{x} - \left(\frac{y}{x} \right)^2 & \frac{x}{y} > 1, \end{cases} \quad (\text{D56c})$$

which can be shown by Taylor expanding all the functions in Eqs. D27, D40, and D41 for small $\frac{1}{z}$ and evaluating. Utilizing the same method for the other instances of $\lambda(0)$ in Eq. D55 allows it to simplify to

$$\begin{aligned} \lim_{\lambda(0) \rightarrow \infty} \frac{(\delta m_j)^2}{\bar{m}_j^2} &= \frac{1}{\beta T} \left(\sum_l \bar{r}_l \Lambda_\infty \left(\frac{|\vec{x}_l - \vec{x}_j|}{a} \right) \right)^{-2} \left(\sum_s \bar{r}_s \left(\Lambda_\infty \left(\frac{|\vec{x}_s - \vec{x}_j|}{a} \right) \right)^2 \right. \\ &\quad + \sum_{s,u} 2\alpha\beta\bar{c} \lim_{\omega \rightarrow 0} \left(\frac{1}{\omega} \text{Im} (R_{su}^{-1}(\omega)) \right) \Lambda_\infty \left(\frac{|\vec{x}_s - \vec{x}_j|}{a} \right) \Lambda_\infty \left(\frac{|\vec{x}_u - \vec{x}_j|}{a} \right) \\ &\quad \left. + \sum_s 4\bar{r}_s \left(\frac{1}{18} \Upsilon_\infty \left(\frac{|\vec{x}_s - \vec{x}_j|}{a} \right) + \frac{1}{9} \Xi_\infty \left(\frac{|\vec{x}_s - \vec{x}_j|}{a} \right) \right) \right) \end{aligned} \quad (\text{D57})$$

For the two cell case Eq. D55 can be further evaluated. Let $\ell = |\vec{x}_1 - \vec{x}_2|$. Utilizing Eqs. B21 and B22 to evaluate R^{-1} and the knowledge that $\bar{r}_1 = \bar{r}_2 = \bar{r}$ then yields for either cell

$$\begin{aligned} \frac{(\delta m)^2}{\bar{m}^2} &= \frac{1}{\beta T} \left(1 + \Lambda_\infty \left(\frac{\ell}{a} \right) \right)^{-2} \left(\frac{1}{\bar{r}} \left(1 + \left(\Lambda_\infty \left(\frac{\ell}{a} \right) \right)^2 \right) \right. \\ &\quad + \frac{2\alpha\beta\bar{c}}{\bar{r}^2} \left(\frac{1 + \text{Re}(\Sigma(0,0))}{\mu^2} \left(1 + \left(\Lambda_\infty \left(\frac{\ell}{a} \right) \right)^2 \right) + 2 \frac{\text{Re}(\Sigma(\ell,0))}{\mu^2} \Lambda_\infty \left(\frac{\ell}{a} \right) \right) \\ &\quad \left. + \frac{2}{9\bar{r}} \left(3 + \Upsilon_\infty \left(\frac{\ell}{a} \right) + 2\Xi_\infty \left(\frac{\ell}{a} \right) \right) \right) \end{aligned} \quad (\text{D58})$$

Utilizing the relation between \bar{r} and \bar{c} in Eq. B2 as well as the explicit form of $\Sigma(\vec{x}, 0)$ in Eqs. B6 and B7 (again setting $g = 4$) allows Eq. D58 to be simplified to

$$\begin{aligned} \frac{(\delta m)^2}{\bar{m}^2} &= \frac{1}{\pi a \bar{c} D_c T} \frac{1 + \left(\Lambda_\infty \left(\frac{\ell}{a} \right) \right)^2 + 2 \frac{a}{\ell} \Lambda_\infty \left(\frac{\ell}{a} \right)}{2 \left(1 + \Lambda_\infty \left(\frac{\ell}{a} \right) \right)^2} + \frac{1}{\mu \bar{r} T} \frac{2 \left(1 + \left(\Lambda_\infty \left(\frac{\ell}{a} \right) \right)^2 \right)}{\left(1 + \Lambda_\infty \left(\frac{\ell}{a} \right) \right)^2} \\ &\quad + \frac{1}{\beta \bar{r} T} \frac{\frac{5}{3} + \left(\Lambda_\infty \left(\frac{\ell}{a} \right) \right)^2 + \frac{2}{9} \Upsilon_\infty \left(\frac{\ell}{a} \right) + \frac{4}{9} \Xi_\infty \left(\frac{\ell}{a} \right)}{\left(1 + \Lambda_\infty \left(\frac{\ell}{a} \right) \right)^2} \end{aligned} \quad (\text{D59})$$

The first term is as in the main text. Let \bar{r} be large enough such that the second two terms in Eq. D59 can be neglected. Additionally, assume $\ell > a$. Under these, Eq. D56a can be used to reduce Eq. D59 to

$$\frac{(\delta m)^2}{\bar{m}^2} = \frac{1}{\pi a \bar{c} D_c T} \frac{1 + \left(\frac{2a}{3\ell} \right)^2 + 2 \frac{a}{\ell} \frac{2a}{3\ell}}{2 \left(1 + \frac{2a}{3\ell} \right)^2} = \frac{1}{\pi a \bar{c} D_c T} \frac{1 + \frac{16a^2}{9\ell^2}}{2 \left(1 + \frac{2a}{3\ell} \right)^2} \quad (\text{D60})$$

The coefficient of $\frac{1}{\pi a \bar{c} D_c T}$ in Eq. D60 achieves its minimum value of $\frac{2}{5}$ at $\ell^* = \frac{8}{3}a$, which is within the bounds of the $\ell > a$ assumption.